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MEDICAL RESEARCH COUNCIL

A STUDY OF EPIDEMIC INFLUENZA: WITH SPECIAL REFERENCE TO THE 1936-7 EPIDEMIC

by
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with
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LONDON
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Universal Decimal Classification
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PREFACE

In 1933 the study of influenza received an important stimulus from the work of Sir Patrick Laidlaw, Dr. C. H Andrewes and Dr. Wilson Smith, in the service of the Medical Research Council at the National Institute for Medical Research The discovery which reopened this field of investigation to experimental research was, essentially, that the infection from human cases diagnosed as influenza could be transmitted to ferrets, in which it caused a characteristic feverish and catarrhal condition ; this condition was transmissible to other healthy ferrets, and recovered ferrets were immune for the time being against further infection. Later it was shewn also that mice,

disease, indicated that the causative organism was of the nature of

and recovered from the disease, and further infection of ferrets and mice by washings from his nasopharynx, left no doubt as to the nature of the infecting agent in both man and animals

While this work on the causation of influenza was being confirmed and extended, other investigations were already directed to possible means of preventing the disease Even by the end of 1935, experiments on laboratory animals had given grounds for hope that successful prophylaxis, against the virus strains available for study at that time, was within sight It was apparent, however, that a satisfactory application of such methods to human beings must largely depend upon the possibility of demarcating cases of influenza of virus ætiology from other diseases with similar symptoms Correlated clinical and laboratory studies were clearly necessary

These correlated studies were begun early in 1936 Dr C H

was in close and constant association with Dr Andrewes and Dr Wilson Smith, who were responsible for the experimental side of the work Through the courtesy of the medical staffs of the Royal Navy, Army, and Royal Air Force, facilities were granted for the study of influenza cases at a number of Service Hospitals Early in 1936 various outbreaks of respiratory disease resembling influenza were studied, from them no virus was recovered Towards the end of the year, and at the beginning of 1937, a more widespread epidemic occurred from which virus was recovered, repeatedly and with ease These various outbreaks of acute respiratory disease, some of unknown ætiology and some of proven virus origin, constitute the basis upon which the attempt is made in the present report to characterise influenza due to virus infection The other conditions, simulating influenza, are designated "febrile catarrhs"

It is clear that a means of differentiating epidemic influenza febrile catarrh by clinical examination only, and independentl determining the presence or absence of the influenza virus, wo constitute an important advance in the study of these proble Among other differences, Dr. Stuart-Harris found that whereas onset of epidemic influenza is usually sudden, in febrile catarrh it often insidious; that in influenza constitutional symptoms p dominate, while in febrile catarrh respiratory symptoms are mo common; that the cough in influenza is short and dry, while i febrile catarrh it is more often paroxysmal, irritating, painful an productive. While such differences allow fairly good means o diagnosis in the case of groups of patients, they are by no means as certain in the diagnosis of the condition in individual patients. So, although these combined clinical and laboratory investigations have clarified the problem to be solved, they cannot yet be regarded as having provided the medical practitioner with a certain method of differential diagnosis by clinical examination alone. The distinction between the two conditions will obviously acquire great practical importance if a means of dealing with one of them should be found, of such a kind that it is inapplicable to the other. A method based on specific immunity to the influenza virus cannot be expected to have any useful action against different organisms.

The difficulty of differentiating influenza from febrile catarrh by clinical examination is only one of the major problems studied in the present work. A second is presented by the antigenic differences amongst strains of the influenza virus which may exist even in the same epidemic. The laboratory investigations of the various strains of virus isolated during the 1936–37 epidemic confirmed the discovery of Magill and Francis, in America, that such antigenic differences exist among virus strains of human origin. This fact, however, was unknown at the time when the prophylactic experiments on army volunteers were planned and carried through, and it may in part explain the disappointing results described in the final section of this report.

The work has resulted in the accumulation of many new facts concerning not only the virus strains isolated, but also the artificial immunization of experimental animals and the antibody status of the human population in relation to epidemic influenza. These, besides being of interest in themselves, indicate the lines of work which hold out promise for the eventual solution of the problem of the prevention and specific treatment of the disease.

The Council are glad to be able to publish this comprehensive account of the combined clinical and experimental investigations made during the influenza epidemic of 1937. The work described forms part of the sustained and systematic effort initiated at the National Institute of Medical Research to solve the problem of epidemic influenza, and it clearly represents a substantial advance on the way to the ultimate control of this disease.

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With Special Reference to the 1936–7 Epidemic

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INTRODUCTION

The few years which have elapsed since a filterable virus was first isolated from cases of influenza have been particularly fruitful in investigations on this disease carried out in many different countries. It has now been abundantly established that a virus, initially pathogenic for the ferret and subsequently adaptable to [illegible]

to recover virus during certain small localized epidemics and from many cases occurring sporadically but diagnosed as influenza have been recorded. There are many possible explanations of these apparently contradictory results, the most probable being that several diseases with clinical similarity but different aetiology masquerade under the common term "Influenza," the indiscriminate use of which term as a diagnosis for almost any pyrexia of unknown origin is notorious.

In 1935 it was decided that correlated clinical and laboratory [illegible] epidemics of respiratory disease [illegible] of delimiting a disease entity [illegible]

The clinical studies were carried out on cases occurring during four localized epidemics from which no virus was recovered and during several outbreaks in different localities during the recent 1936-7 epidemic from which many virus strains were isolated. Most of the investigations were made in hospitals belonging to the Army, Navy and Air Force and were only rendered possible by the kind co-operation of the medical staffs of these Services. In particular, thanks are due to Surg Rear-Admiral F Sheldon Dudley, O B E, R N, Maj-Gen H Marrian Perry, C B, O B E., K H.S, R A.M C, and Air Commodore W Tyrrell, D S O, M C, R A.F. Med Br., who were most helpful in facilitating these investigations. At the several hospitals, Surg Rear-Admiral B Pickering Pick, O B E., R N, Surg-Capt H B Parker, D S C, R N, Surg.-Capt J Gordon Danson, R N, and the staff of the medical division of the Royal Naval Hospital, Surg Lt-Cdr W P E McIntyre, R N., Colonel E D Anderson, Roy Horse Guards, Lt-Col L Dunbar, O B E, R A M C, Maj C R Christian, R A M C, Maj H L Mann, M C, R A M C, Maj A Mearns, R A M C, Maj L M Rowlette, D S O, H W Corner, R A M C, Lt-Col F C K Austin, R A M C, Wing Commander Med Br and Flight Lt O S M Williams, R A F Med Br, took a personal interest in the work and assisted in ways that are too numerous to mention, they were unfailingly helpful in spite of the fact that the normal routine of the hospital was interfered with at a time when, owing to the epidemic, extra work was thrust upon all members of the staff

The following have also co-operated with us in this investigation, and to them we wish to extend our grateful thanks —Prof F R Fraser, Drs F Griffith R E Smith, R Riley, P H Wood, J G Scadding, A B Rosher and P B Wilkinson

The type of population studied was admittedly a selected one In the Service depots where the outbreaks occurred the population consisted of young adults chiefly between the ages of 17 and 21, there being an unusually high proportion of recruits who had recently joined the Services owing to the present expansion programme The men were living under conditions very different from those of civil life, being housed in barracks, and it is conceivable that such conditions might have modified the severity of the infection Furthermore 40 per cent of the patients lived in country districts before joining the service and 44 per cent came from urban districts other than large towns a fact which found expression in their past histories for many of them denied any previous illness, even including the infectious fevers There were, however, definite advantages in choosing a military or naval rather than a civil population in which to study the clinical picture of influenza The patients were all healthy and physically fit prior to the illness so that the picture seen was unmodified by previous or concomitant disease processes Cases were admitted to hospital much earlier than they would have been in civil life so that the whole clinical course was available for

study. Again the milder grades of illness which would ordinarily

tion of the general types of illness occurring in this country and diagnosed as "influenza."

The laboratory investigations have necessarily taken many different directions. In direct connection with the clinical studies attempts were made to isolate virus from representative cases in each outbreak. The 1936-7 epidemic provided no fewer than 39 new virus strains. A detailed antigenic analysis of these was necessitated by the recent discovery of Magill and Francis (1936) that certain virus strains, which previously had been regarded as antigenically identical, proved upon more searching examination to show certain differences. This part of our work is still very incomplete but enough has been done to establish the importance of taking into account strain variations in any further efforts to induce immunity to influenza by prophylactic vaccination.

human and swine strains of virus, occur in the sera of a high percentage of the human population but the frequency of their occurrence varies in different age groups. One section of this report deals especially with our further studies on the relationships existing between antibody level on the one hand and infection, susceptibility, epidemic explosion and contact with infectious cases on the other.

Another section comprises the logical extension of previous work which showed that both ferrets and mice can be successfully immunized against experimental infection. It had long been felt that groups of volunteers should be vaccinated during a period of influenzal quiescence so that the effect of the vaccination might become manifest whenever a widespread epidemic should occur. Although vaccination with living virus had already been practised in U.S.A. without untoward results (Francis and Magill 1936a, 1937a; Stokes *et al.* 1937), it appeared to us desirable first to extend the experiments with lower animals in order to obtain a vaccine in which the virus was inactivated and from which as much as possible of the undesirable constituents like animal proteins had been eliminated. These objects were to a large extent attained but unfortunately not until immediately before the onset of the recent epidemic. Numbers of volunteers were in fact vaccinated but although they yielded information of value, they failed to provide a clear-cut demonstration of either the efficacy or the non-efficacy of the vaccine employed. However, both the information and the experience gained during this preliminary field trial will undoubtedly be useful when a future epidemic provides another opportunity for the study of prophylactic vaccination of human beings.

SECTION I

CLINICAL STUDIES ON OUTBREAKS RESEMBLING EPIDEMIC INFLUENZA

By C. H. Stuart-Harris

A.—The Woolwich Epidemic, February, 1936

1.—Epidemiological Data

During February and March, 1936, epidemics of a respiratory disease occurred at several military depôts in London, the largest outbreak being at Woolwich. Here the Royal Artillery Barracks and Military College of Science were involved, patients being admitted to the Royal Herbert Hospital. Detailed figures for the different areas are not available, but some 300 patients were admitted to the hospital between February and April, and most of these came from Woolwich, where the garrison housed 3,200 men and boys. Not more than 10 per cent. of the population was, therefore, involved and the epidemic lasted for about 10 weeks, with a more or less steady stream of patients during the first 6 weeks. Detailed notes were made on 41 patients between the ages of 14 and 24, and on one man of 35 years of age. The disease apparently had a higher incidence among the youngest age groups in the garrison and among recruits, but there are no figures available. With regard to the type of population, remarks made in the introduction apply to the Woolwich epidemic, that is, the population was selected, being composed of young healthy adults with little previous disease. Of the 42 patients 16 had had "influenza" before, 7 had suffered from tonsillitis, 13 admitted frequent colds, and only 4 patients had had lower respiratory disease such as pneumonia and bronchitis.

2.—Clinical Features

The 42 cases fell into 3 groups:—

(a) Uncomplicated cases (29).
(b) Cases complicated with "basal bronchitis" (9).
(c) Cases complicated with pneumonia (4).

(a) *The Uncomplicated Cases*

The majority of the patients suffered a short febrile illness similar in its symptoms in some respects to epidemic influenza. In some patients the disease was clearly a tonsillitis and was so diagnosed, but in others the faucial inflammation was accompanied by laryngitis and tracheitis and in these the diagnosis was "influenza." At the time, this being the first epidemic of "influenza" to be studied clinically, the significance of the cases of tonsillitis was missed. It was assumed that in any large group of men and boys living under barrack conditions tonsillitis was bound to occur from time to time, especially during the winter months. The cases of tonsillitis in the epidemic

were, therefore, regarded as an incidental accompaniment rather than a part of the epidemic. Now subsequent clinical experience, and retrospective study of the notes, has shown that tonsillitis is an integral part of this type of epidemic and that cases of tonsillitis, including some with definite streptococcal infection, occur side by side with cases suggestive of "influenza." Among the group of 29 patients there were three who might have been diagnosed clinically with the support of bacteriological evidence as streptococcal tonsillitis. Yet the clinical picture in these three was not so different from that in the rest of the group as to warrant its separation. Then there was a number of mild cases of febricular or one-day fevers with atypical symptoms and signs and one, a febrile patient, was studied. Symptoms in the latter comprised cough and sore throat; physical signs were negligible, but the patient was a close contact of other, typical, cases.

(i) *The typical picture*

After an insidious onset with vague malaise, cough or coryza, there was a sudden development of illness with sore throat. The next day shivering occurred, headache developed, there was pyrexia, and the throat was even more sore. The temperature was raised for about 4 days, being at its height for the first two, during which the appearance of the patient was striking. There was a bright facial flush, cyanosis of the lips, and a frequent irritating cough, dry at first, but later accompanied by mucopurulent expectoration. The nose was obstructed or discharging, the voice hoarse, and the fauces moist and injected, with swelling and reddening of the tonsils and a loose mucopurulent exudate. The chest showed no abnormal signs during the whole illness. Complaint was chiefly directed to the sore throat and the cough, but substernal soreness across the front of the chest was common. Once the temperature reached normal, the patient felt quite well and convalescence was rapid, cough being the last symptom to disappear.

(ii) *Detailed analysis of the symptoms and signs in 28 febrile patients*

The onset.—Premonitory symptoms occurred in 8 patients with cough, coryza, or malaise for a week or more before the onset of illness. The latter was described as sudden in 12 patients (42 per cent.), the rest having a more insidious development of illness. This fact is well shown by the day of disease on which the patient was admitted. Only 2 patients were admitted on the 1st day, 8 on the 2nd day, 8 on the 3rd, and the remainder (10) were admitted from the 4th to the 8th day after the onset of symptoms. Table 1 shows the first symptoms that were complained of in order of frequency. Sore throat heads the list, being the first symptom in 12 patients, then come cough, coryza, headache, dizziness, shivering, muscular pains and malaise. The three symptoms arising from the respiratory tract thus preceded constitutional symptoms at the beginning of the disease.

TABLE 1

Epidemics resembling influenza

Symptoms at onset	*Per cent*	*Symptoms during course*	*Per cent.*
Sore throat	42	Cough	86
Cough	35	Malaise	82
Coryza	21	Sore throat	80
Headache	17	Anorexia	
Dizziness	14	Shivering	70
Shivering	10	Coryza	
Muscular pains	7	Headache	64
Malaise	3	Dizziness	
		Muscular pains	53
		Sweating	
		Expectoration	50
		Insomnia	
		Hoarse voice	40
		Pain in the chest	
		Abdominal pain	
		Vomiting	28
		Constipation	
		Ocular symptoms	
		Epistaxis	21
		Diarrhoea	
		Nausea	3
		Faint feeling	

Symptoms —Table 1 also shows the percentage frequency of the symptoms during the whole course of the disease

General or constitutional symptoms did not dominate the clinical picture as in epidemic influenza but, when present, they occurred at the height of the pyrexia

Malaise —This was definite in 20 out of the 28 patients and slight in 3 others (82 per cent altogether) but it was never severe Patients would always admit that they felt ill if questioned yet they rarely complained of this

Headache —Frontal headache was definite in 15 of the 28 patients, and slight in a further 3 It was rarely severe and never persistent beyond the first 24 hours after admission

[illegible]

the patient was put to bed

Dizziness —Eighteen patients complained of this before admission

Muscular pains —Backache was noted by 8 patients, always before admission and muscular pains elsewhere by a further 7 53 per cent in all Pains were never severe but were quite definite

Sweating —Sweating was noted by 14 patients before admission and usually accompanied defervescence being profuse at times

Less common symptoms were [illegible]

[illegible]

before admission

Ocular Photophobia or pain on movement of the eyes occurred in only 6 patients in all There was no complaint of diffuse aching of the eyes

Insomnia —A restless night on one or more occasions prior to admission occurred in 11 patients

Symptoms arising from the respiratory tract were constant and dominated the clinical picture.

Coryza —A running nose had been noticed by 19 patients before admission, while actual coryza was observed 8 times It was in each case typical of a common cold, being first a watery discharge, then mucopurulent and finally purulent In 8 patients the nose was considered to be a little obstructed Epistaxis had occurred in 4 patients before admission and in 2 more after admission. It was sometimes severe and repeated.

Sore throat.—This was an early and frequent symptom (22 patients). There was no disparity between faucial signs and symptoms

Hoarseness of the voice —A husky voice was observed in 10 patients while 11 others had a definite hoarse voice Further, hoarseness of the voice was commonly volunteered by the patient as a troublesome symptom.

Cough —Cough was present in all except one patient, though it was only slight in 3 In the majority of patients it was the most prominent symptom being frequent, paroxysmal, and rasping or tearing. In patients with laryngitis it was barking in character The wards containing the[illegible] noisy because of the incessant cough [illegible] worse on coughing wa[illegible]

Sputum —[illegible] sputum was [illegible] not usually appear till th[illegible] when a little green tenacious mucus was ex[illegible] volume increased and might become considerable with nummules of mucopus The sputum was streaked with blood on rare occasions In spite of the expectoration, abnormal signs were not necessarily found in the chest

The combination of irritating cough, substernal soreness and expectoration without signs in the chest was a prominent feature of the epidemic disease now being described, and was considered to be evidence of a tracheitis

The fever —After admission the temperature was raised for about 3 days on the average and then fell sharply to normal In 6 patients there was one day of fever, 3 had two days, 8 had three days and 11 had four to six days The duration did not differ on the average in those patients with a previous history of " influenza " from those without such history The temperature peak at the height of the fever was 104° F in 3 patients, 103° in 7, 102° in 10 and 101° or less in 8 The character of the fever can be variously described as remittent (8), a steadily diminishing temperature from the day of onset (5), a single spike (4), a double spike, diphasic in type (3), and continued (2) On the whole, therefore, a diphasic type of fever was not a special feature of this epidemic although it was noted in about 10 per cent of patients

The pulse rate was characteristically raised in concordance with the temperature (70 per cent) but a relative tachycardia (18 per cent) or relative bradycardia (12 per cent) also occurred. The respiration rate was never raised and there was no dyspnoea

Physical signs —The patient on admission was pale with a drawn look, the hands and lips being slightly cyanosed After a few hours when the temperature had risen, the face was strikingly flushed and bright red in colour, the lips remaining mauve The flush involved

forehead and cheeks, avoiding the circumoral area, and did not usually appear on the trunk and limbs. So long as the temperature remained high there was some degree of flush, and during convalescence it was observed that a flush might arise again on the least provocation, suggesting an unstable vasomotor control. In 11 of the 28 patients the conjunctivae were injected or more glistening than normal, but the appearance was not striking. The mentality was always alert, with a normal reaction time.

There was sometimes coryza with reddening of the upper lips and around the nares as in the common cold, and the nose was sometimes blocked, but nasal signs were only noticed in 13 patients after admission The upper lip showed herpes in one patient. The tongue was sometimes clean and moist, even in patients with high fever, but in 11 it was coated with a white fur

The throat was abnormal in all except 1 patient There was injection of the fauces involving the capillaries, so that the general appearance was as though the whole fauces, including the posterior part of the soft palate, uvula, and tonsils, had been painted bright red When present, the tonsils were much swollen with prominent crypts, while the lymphoid tissue on the posterior pharyngeal wall was also swollen and red Exudate was present on the tonsils in 7 instances It was typically follicular in 3 patients, and in the remainder comprised a loose flocculent exudate apparently composed of mucopus smeared over the fauces Greenish mucopus running down from the postnasal space was present in a further 4 patients Enlargement of the tonsillar lymph glands was present in 14 of the patients but it was considerable only in 4, whose glands were also a little tender No suppurative adenitis occurred Laryngitis was definite in 11 patients and hoarseness of the voice persisted during the first few days of convalescence

Abnormal physical signs were detected in the chest in 9 patients (33 per cent), comprising scattered rhonchi in 4 and a patch of râles at one base in 5 They were not persistent and were usually noted on one occasion only Sputum has been described under symptoms, and it is worth while emphasizing here that it was present in 14 patients (50 per cent), including 5 who showed no abnormal physical signs in the chest

The heart was normal on clinical examination and the blood-pressure was within normal limits during the fever, the average for 11 patients being 115 70 The abdomen was normal , the reflexes were normal in 7 patients in whom they were examined , there was no albumin in the urine of the only 2 patients in whom it was examined Sinusitis, otitis media, or quinsy did not occur in any of the patients studied During the epidemic one or two cases of otitis media followed by mastoiditis did occur, although the patients were not seen by us

Convalescence Convalescence was rapid and strength was regained as soon as the temperature became normal Hoarseness of the voice, cough and slight sputum were the last symptoms to

disappear. The patients did not appear depressed and were fit for discharge by the 8th or 9th day.

(iii) *Illustrative case*

96 and the respiration rate 20. February 6th: Temperature was now 104° F. and the pulse rate 108, the patient was flushed and the lips were slightly

February 7th Temperature remitted but rose in the evening There was frequent cough of a barking type with substernal pain but the chest was normal on examination February 8th: Temperature now normal, the patient felt well, there was a little viscid mucopurulent sputum February 9th · Convalescent and feeling quite well.

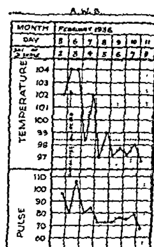


Chart I.

The leucocyte count was 10,000 per c mm on February 6th, 5,200 on February 10th, the differential leucocyte count showed slight increase in monocytes on the first occasion. A ferret was inoculated with garglings collected on February 6th and remained normal Culture of the sputum showed Gram-positive cocci, *M catarrhalis* and a very few colonies of Pfeiffer's bacillus

(b) *Cases Complicated with Basal Bronchitis*

In 9 of 28 patients abnormal signs in the chest were definite and ... similar to ... nts ... or

cough and sore throat had occurred in all but ... This means that the patients were admitted at a later stage of the illness, a factor

perhaps connected with the development of chest complications
In 7 patients the illness was a remittent fever of three to eight days

chest signs appeared and then disappeared, only to reappear later with a fresh rise of temperature.

Cough was invariable and of the irritating, paroxysmal type during the first day or two after admission, it then became productive with sputum; the latter was green or yellow-green in colour, frothy, mucopurulent, and streaked with blood in two cases. It was very abundant, amounting to several ounces a day in 6 patients. The abnormal physical signs consisted of added sounds, usually fine or medium râles, abundant in number, and heard at one or both bases and in one case over the mid-zone of the lung Rhonchi were also heard in 3 patients Impairment of percussion note was slight only; accompanied by a little diminution in volume of the breath sounds, it was noted in three patients There was nothing in the nature of suppressed breathing, and the voice sounds were normal. Signs of pleurisy were not elicited The respiration rate was raised to 30 in three patients, but there was no dyspnoea

These signs were believed to indicate an inflammation of the fine bronchi and bronchioles Unfortunately radiograms were not taken on these patients and judgment must be made on clinical grounds. There was no reason to suspect an extension of the inflammatory process to the alveoli, for breath sounds were usually unaltered and percussion note unchanged Further there was catarrh of the bronchi as indicated by the abundant râles and also by the sputum The term "basal bronchitis" has been used deliberately because it is believed that a distinction exists between this condition and that seen in epidemic influenza and termed "bronchiolitis" These terms are, however, used as labels for different clinical conditions and it must be recognised that the difference between the underlying pathological processes has not yet been determined.

Illustrative case *Case* 2—R W aged 14, had had a cough for a week before admission on February 6th, 1936 He had been dizzy at times with [illegible]

were slightly cyanosed There was coryza with a good deal of mucopurulent sputum The voice was hoarse the nose normal and the fauces injected [illegible]

and medium râles at the right base Cyanosis was more marked on this day and the [illegible]

Better [illegible]

sputum [illegible]

Signs in [illegible]

otherwise convalescent February 20th: Feeling quite well although voice still a little hoarse. The patient flushes easily at times, and the lips are also slightly cyanosed occasionally

A leucocyte count on February 6th showed 7,200 per c.mm., on the 7th 6,400 per c mm. and on the 10th 5,600 per c mm.; the differential leucocyte picture was within normal limits Sputum collected on February 7th was inoculated into a ferret but the animal remained normal Culture of the sputum showed a predominance of *H. influenzae* and *M. catarrhalis*

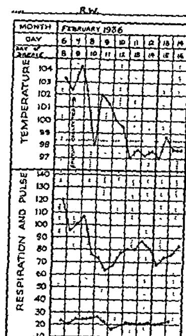


Chart 2

(c) *Cases Complicated with Pneumonia*

There was one patient with lobar pneumonia admitted from Chelsea at the time of the epidemic at Woolwich, who presented the typical onset, symptoms and signs, and course of lobar pneumonia. His case was studied in order to furnish a contrast with the three patients in whom consolidation of the lungs was suspected but not proved The first of the latter group was a man, a close contact of

normal, though the signs in the chest did not wholly disappear. The sputum was purulent, abundant in amount, and yielded *M. catarrhalis* and *H influenzae* on culture On the 9th day after admission there was a sharp relapse with pain in the left side of the chest on breathing. There was pleural friction over this area while a radiogram showed slight opacity behind the heart extending laterally. Empyema developed and was drained, the patient responding well to treatment.

Culture of the pus from the empyema gave a pure growth of a haemolytic streptococcus. Thus, then, was a case of capillary bronchitis with a small patch of bronchopneumonia unsuspected clinically, in which there developed a streptococcal empyema.

The next patient was ill for nearly three weeks and finally died. He presented a typical picture of the epidemic disease on admission with coryza, tonsillitis, laryngitis and scattered bronchitis. Following slight improvement by the 7th day after admission, relapse occurred; râles and rhonchi developed at the bases and the breath sounds became faintly bronchial. The condition at the bases appeared to be a patchy bronchopneumonia to which the patient slowly succumbed. There was a history of several previous attacks of pneumonia in his childhood. The leucocyte count was 10,000 c.mm. initially, falling to 6,400 before death. There was no post-mortem.

The third patient, who also died, was a man whose condition recalled the accounts in the literature of purulent bronchitis (Abrahams, Hallows, Eyre and French, 1917; Hammond, Rolland and Shore, 1917). Admitted on the 7th day after the onset of a cold and a cough, he was very dyspnoeic, coughing frequently and expectorating pus, and had a livid collapsed appearance. There were few signs of upper respiratory catarrh, the chest showed generalized rhonchi with bubbling râles at the bases, the pulse rate was 120, the pulse was feeble with pulsus alternans, and the heart showed a gallop rhythm with a fluttering diffuse impulse. Improvement occurred after admission but the patient died the next day. Although the respirations were distressed, being almost asthmatical in type shortly before death, their rate was not increased. Post-mortem was not permitted. The leucocyte count was 23,000 shortly before death, there being a polymorphonuclear leucocytosis. Cultivation of the sputum had yielded *H. influenzae* and *M. catarrhalis*. This man was a contact of other cases typical of the epidemic disease.

Thus the upper respiratory catarrh typical of the Woolwich epidemic was associated at times with involvement of the lower respiratory tract. The trachea was involved, then the bronchi and the bronchioles and sometimes, though rarely, the alveoli. The picture thus produced was that of a capillary bronchitis, or a basal bronchiolitis or a bronchopneumonia. Signs of frank consolidation of the lungs, such as occur in influenzal pneumonia, did not develop. It is a pity that radiograms were not available in all the cases of bronchopneumonia which were seen in this epidemic, but the only one which was taken showed a small area of opacity at one base.

3.—PATHOLOGICAL INVESTIGATIONS

(a) *Attempts to Recover Influenza Virus*

Garglings were taken on the 3rd day from 3 patients with the uncomplicated disease and on the 4th day from another. They were inoculated into ferrets, which developed no disease and were subsequently susceptible to inoculation with the W.S. strain of influenza

virus. Samples of sputum from two cases of capillary bronchitis on the 3rd day after admission were also non-pathogenic for ferrets. Garglings on the 3rd day of illness of the patient who developed typical lobar pneumonia were non-pathogenic for a ferret and contained pneumococci. Influenza virus was not recovered, therefore, from this epidemic.

(b) *Examination of Sera for Influenzal Antibodies*

Four men were bled, 3 in the acute and convalescent stage and 1 in the acute stage only. Three were cases from which an attempt was made to recover virus. None of the men showed any rise in antibody content as a result of the infection, all the sera having poor neutralizing properties for influenza virus. This result agrees with the inability to recover virus and is good evidence that the virus was not concerned in the infection.

(c) *Bacteriological Investigations*

Twelve throat swabs and 20 sputa were cultured on blood agar and the results of the cultures so far as haemolytic streptococci, pneumococci and Pfeiffer's bacillus were concerned are shown in Table 2. Gram-negative cocci resembling *M. catarrhalis*, diphtheroid bacilli, non-haemolytic streptococci and *Streptococcus viridans* were isolated from most specimens. Pfeiffer's bacillus and a Gram-negative coccus were the predominating organisms particularly in the sputa. Eleven strains of Pfeiffer's bacillus were shown to be haemophilic and were then handed over to Dr. A. B. Rosher who

TABLE 2

Woolwich epidemic (resembling influenza)

Results of cultures of throat swabs and sputa

		Pneumococci	*H influenzae*	*Haemolytic streptococci.*	
				Number positive	*Per cent of total flora*
Straightforward cases—					
Throat swabs	10	2	5	4*	90 p c in 2; less than 1 p c in 2.
Sputa	9	0	8	1	10 p c
Basal bronchitis—					
Throat swab	1	0	0	1	10 p c
Sputa	7	2	7	0	
Bronchopneumonia—					
Sputa	2	0	2	0	
Empyema pus	1	0	0	1	100 p c
Lobar pneumonia					
Sputa	1	1	0	0	

* Includes three patients with mucopurulent tonsillar exudate and one with follicular exudate. One patient with follicular exudate gave no haemolytic streptococci.

very kindly examined them in detail Dr Rosher reported that half the strains were indole-positive and the rest indole-negative. It was of some interest that Dr. Rosher examined sputa from a number of cases of pulmonary tuberculosis during March 1936; 19 out of 26 of the sputa contained *H. influenzae*, often in profusion.

Pneumococci were not isolated frequently and were never predominating organisms, a fact which contrasts with the frequent occurrence of these organisms in cultures of sputa during the influenza outbreak in 1937 (see below)

Haemolytic streptococci were isolated 7 times. They predominated in the throats of 2 straightforward cases and were the only organism in the pus of the case of empyema In the remaining specimens they were not present in profusion There was no precise relation between the presence or absence of exudate on the throat and recovery of haemolytic streptococci on culture

(d) *Blood Counts*

Leucocyte counts were performed on 5 uncomplicated cases during the fever, on 5 cases of basal bronchitis, on 2 cases of bronchopneumonia and on the one case of lobar pneumonia.

Table 3 shows the results. In uncomplicated cases the counts varied from 5,000 to 11,000 with normal differential counts. Counts on patients with basal bronchitis varied from 5,000 to 14,000 with normal differential counts Of the two patients who died, one had a normal count and the other a polymorphonuclear leucocytosis with absolute increase in monocytes The patient with lobar pneumonia had a polymorphonuclear leucocytosis

4—Discussion

It has been shown that the epidemic, although diagnosed as influenza, was not due to influenza virus infection Indeed no clue

in this epidemic and those seen during the influenza epidemic of 1937, but further discussion must be deferred until the latter have been described.

B.—The Eastchurch Epidemic, May, 1936

1—Epidemiological Data

During May, 1936, an epidemic occurred at the Eastchurch depôt of the R A F, and patients were admitted to the Royal Naval Hospital, Chatham The first few were cases of tonsillitis, one or two exceptionally severe infections occurring with one fatal case, and then there was a group of patients with constitutional reaction out of proportion to the local condition In all, there were 67 cases from a population of 730, but 54 cases were in boys aged 16 or 17, from a group of 150 The remaining 13 cases were in men aged 22 to 30 and were scattered amongst a group of 580 men housed in huts

TABLE 3

Woolwich epidemic (resembling influenza)
Leucocyte counts

Patient	Disease	Day of disease	Total W B C	Polymorphonuclears		Lymphocytes		Mononuclears.	
			Per c mm	*Per cent*	*Per c mm.*	*Per cent*	*Per c mm*	*Per cent*	*Per c mm*
J R D	Straightforward	5th	10,000	67	6,700	22	2,200	11	1,100
"	"	9th	5,000	58	2,900	36	1,800	4	200
E N O	"	4th	11,000	70	7,700	20	2,200	10	1,100
W H	"	3rd	7,000	68	4,760	19	1,330	11	770
L W M	"	4th	9,000	63	5,670	22	1,980	11	990
A S	"	5th	10,000	72	7,200	23	2,300	4	400
R W	Basal bronchitis	6th	7,000	62	4,340	26	1,820	11	770
"	"	7th	6,000	69	4,140	22	1,320	8	480
"	"	10th	5 600	75	4,200	18	1,008	5	280
L G	"	11th	6 000	74	4,440	18	1,080	7	420
H H	"	8th	7,000	80	5,600	14	980	3	210
F M	"	8th	14,000	82	11,480	12	1,680	5	700
C T	"	5th	8,000	67	5,360	28	2,240	5	400
"	"	8th	9,000	74	6,660	19	1,710	6	540
A S	Bronchopneumonia	13th	10,000	64	6,400	26	2 600	8	800
"	"	18th	6,000	65	3 900	29	1,740	0·5	30
E M.	"	9th	23,000	73	16,790	11	2,530	12	2,760
L C T	Lobar pneumonia	5th	18,000	90	16,200	9	1,620	1	180

adjoining the boys' huts Thus there was an incidence of 30 per cent among the boys, and although opportunities for spread of infection to the men existed, less than 3 per cent. of these were affected Scarlet fever had been occurring sporadically in the depôt during March and April and 3 boys developed this during the epidemic. The epidemic lasted one month and showed a peak in incidence in the middle of the month (Chart 3).

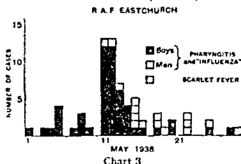


Chart 3

2.—Clinical Features

Detailed notes were made on 12 patients at the Naval Hospital and these comprised 10 cases of pharyngitis or tonsillitis, one of tonsillitis with bronchitis, and one of bronchopneumonia Apart from the patient with pneumonia, the illnesses presented a remarkably uniform picture The onset was sudden, with headache, [illegible] sore throat and pyrexia. Less commonly abdominal pa[illegible]

flushed, and the conjunctivae were injected in six, the nose was a little obstructed in several patients and bled in one the tongue was dirty, and the fauces inflamed The appearance of the latter recalled that seen at Woolwich, there being generalized capillary flushing with swelling of the tonsils and adenoid tissue, and exudate formed on the tonsils in five patients In three, the exudate was yellowish-white and mucopurulent and in two it was discrete, white, and follicular Some degree of enlargement of the tonsillar cervical glands was usually noted, this was especially so in one patient The chest remained normal throughout the fever except in the patient with bronchopneumonia and in one other who developed scattered rhonchi accompanied by slight cough and green sputum. The patient with bronchopneumonia had not been in close contact with other cases of the disease, and showed a short swinging fever for five days accompanied by tonsillitis, and by signs at both bases

consisting of râles, weak breath sounds, and impairment of percussion note on one side. A radiogram showed a dense opacity in the right lower zone which did not extend to either mediastinum or chest wall. The sputum was first frothy and later nummular and green. The respiration rate was normal.

Return of pyrexia with the development of a fresh tonsillitis was seen in four patients. In each case there was exudative tonsillitis and the condition was thought to be a ward re-infection. In support of this were the bacteriological findings.

In the remaining patients there were no complications, the heart and abdomen remained normal throughout, and there were no post-febrile sequelae.

[illegible]

tendency to either relative bradycardia or tachycardia during the fever.

3.—Pathological Investigations

(a) *Attempts to Recover Influenza Virus*

Garglings taken from four patients were inoculated into ferrets. In no case was influenza virus recovered; the garglings tested had been taken on the 2nd, 3rd and 5th days of the disease.

(b) *Examination of Sera for Influenzal Antibodies*

A number of sera taken during the fever and also in convalescence were examined for the presence of influenzal antibodies. In no case did a rise of antibody content follow the fever. Further, a number of other sera taken during convalescence showed low or extremely low levels of antibody content (Table 4). This result agrees with

TABLE 4

Epidemics resembling influenza

Examination of Eastchurch sera for influenzal antibodies

	Febrile	*Convalescent.*	
A A G.	<S/25	<S/25	5 days later.
G H	<S/25	<S/25	4 ,, ,,
V P	S/25	<S/25	9 ,, ,,
K P.	<S/25	<S/25	6 ,, ,,
A M S.	S–S/5	S–S/5	8 ,, ,,
J. C	S	S	8 ,, ,,
V. H B	S/5	<S/5	8 ,, ,,
P D	S/5–S/25	–	
A T	–	<S/25	
I A	–	<S/25	
C V	–	0	
A I	–	<S/25	
B R	–	<S/25	
R C	–	<S/25	
I G	–	S/25	
M W	–	<S/25	

S refers to standard horse serum IH. The method of evaluating sera in terms of that standard will be described later (p 112)

the inability to recover influenza virus from the throat and is good evidence that the virus was not concerned in the aetiology of this epidemic.

(c) *Bacteriological Investigations*

Early in the course of the investigation throat swabs were taken from a number of patients and cultivated on 5 per cent. blood trypsin agar. From a number of the swabs haemolytic streptococci were obtained, and occasionally these organisms preponderated The examination of throat swabs for haemolytic streptococci was continued and Table 5 shows the results in the 12 patients described above and in 3 with relapses Pure strains of the haemolytic streptococci from different patients were typed, whenever possible, by the kind assistance of Dr F Griffith at the Ministry of Health Pathological Laboratory. The results showed that haemolytic streptococci were isolated from 4 out of 10 cases of pharyngitis or [illegible]

high proportion of haemolytic streptococci Among the strains there were three serologically different types of haemolytic streptococci, including Type 19, an organism which did not always give

TABLE 5

Eastchurch epidemic (resembling influenza)

Results of throat swab cultures

Patient	*Disease*	*Day of disease*	*Haemolytic streptococci*		
			Positive	*Per cent. of total flora*	*Griffith's type*
V H B	Pharyngitis	2nd	+	30	? Type 19
G H	"	3rd	0	—	—
L P		4th	0	—	—
K P		4th	0	—	—
V P	Pharyngitis (mucopurulent exudate)	5th and 6th	0	—	—
J C	Tonsillitis (mucopurulent exudate)	2nd and 3rd	0	—	—
	" "	6th	+	10	Type 19
K P G	Tonsillitis (follicular)	2nd	0	—	—
A A G	Tonsillitis bronchitis	4th	0	—	—
R C	Tonsillitis (follicular)	2nd	+	50	Type 3
A M S	Tonsillitis	2nd	+	60	Type 21
P D	Tonsillitis (mucopurulent exudate)	2nd	+	60	? Type 19
A T	Bronchopneumonia	2nd	+	2 colonies	? Type 19
V P	Relapse with exudative tonsillitis	14th	+	75	? Type 19
I G	" "	9th	+	20	Type 19
C V	" "	6th	+	75	Type 3
L A	" "	11th	+	80	Type 19

consistent results with the agglutinating serum. Three of the four relapses were associated with this organism as was the case with a positive swab on the 6th day with previous negative swabs on the 2nd and 3rd day.

(d) *Blood Counts*

Single leucocyte counts were performed on 8 patients (Table 6). The results showed totals varying from 8,000 to 17,000. In this small series there were four who showed a leucocytosis (15,000 or over) with an increase in polymorphonuclear leucocytes and monocytes, and this was not correlated with the presence of haemolytic streptococci in the throat.

TABLE 6

Eastchurch epidemic (resembling influenza)

Leucocyte counts

Patient	Disease.	Day of disease	Total W B.C	Polymorphonuclears.		Lymphocytes		Mononuclears	
			Per c mm	Per cent	Per c mm	Per cent	Per c mm	Per cent	Per c mm
K. P. ..	Pharyngitis	3rd	11,000	60	6,600	30	3,300	9	990
V P .	,, ..	5th	17,000	70	11,900	20	3,400	8	1 360
E P	,,	3rd	16,800	50	8,400	42	7,056	7	1,176
G. H ..	,, ..	4th	10 000	66	6 600	23	2,300	9	900
K. P G	Tonsillitis	3rd	16 000	70	11,200	16	2,560	12	1,920
A. T	Broncho-pneumonia	3rd	10,000	68	6,800	25	2,500	6	600
A A G*	Tonsillitis and bronchitis	3rd	8 000	78	6,240	15	1,200	6	480
P D*	Tonsillitis	3rd	15 000	80	12,000	9	1,350	9	135

* Haemolytic streptococci predominated in the throat flora.

4.—DISCUSSION

This epidemic has been shown to be aetiologically unconnected

examined in the acute stage throw doubt upon this view. For six out of ten patients yielded no haemolytic streptococci during the acute stage, although this organism was recovered during a relapse or after the patient had been in the ward for some days. It seems clear that the relapses represented ward re-infections with the various haemolytic streptococci present in the throats of some of the patients on admission Another important point was that haemolytic streptococci were not isolated from the throats of three patients with an exudative tonsillitis, and this experience recalls that of the Woolwich epidemic The epidemic was, therefore, one of cases of pharyngitis or tonsillitis intermingled with frank streptococcal tonsillitis

C.—The Chatham Epidemic, November, 1936

1.—Epidemiological Data

During November and early December, 1936, the Royal Naval Hospital, Chatham, admitted a number of patients from the naval barracks where an epidemic of "common cold" and "tonsillitis" was occurring. The epidemic reached a climax on December 1st, but the admission rate had been above normal winter levels during the previous two weeks. A combined chart of the November out-

2.—Clinical Features

The clinical picture of the November epidemic recalled that of the Woolwich outbreak. The "common cold" was a coryza with a pharyngo-laryngo-tracheitis Symptoms comprised headache, coryza, sore throat, hoarse voice and most important of all, a painful irritating cough Expectoration was less frequent than at Woolwich, and the striking facies seen there was only occasional at Chatham. Besides the frequent cough of the "tracheitis" type, resemblance between the epidemics was strengthened by the occurrence of a number of cases of "basal bronchitis" and a few of bronchopneumonia These cases were very similar to those seen at Woolwich and had the same type of mucopurulent sputum although there were fewer cases with abundant expectoration The onset of the disease was insidious and patients were admitted to hospital several days after the beginning of the disease Among the group of patients diagnosed as "common cold" and comprising a pharyngo-laryngo-tracheitis there were some diagnosed as "tonsillitis" These patients showed very flushed throats and swollen tonsils with a follicular or mucopurulent exudate They suffered from laryngitis and painful cough as did the other patients and could not be justifiably separated on clinical grounds

3.—Pathological Investigations

(a) *Attempts to Recover Influenza Virus*

Garglings were collected from 3 patients on admission to hospital and inoculated into ferrets The days of illness on which the specimens were collected were the 3rd, 4th and 5th, owing to the insidious onset of the illness Influenza virus was not recovered from any of the specimens

(b) *Examination of Sera for Influenzal Antibodies*

Sera from 2 patients in the acute and convalescent stage, and from two others in the convalescent stage only, were examined for neutralizing antibodies to influenza virus None showed any appreciable amount of antibody, nor was there any rise after the infection

(c) *Bacteriological Investigations*

The 3 garglings, 12 throat swabs and 3 sputa were cultivated o 5 per cent. blood trypsin agar for the detection of haem... tococci. Table 7 shows the ... patient

1 ... pneumococci and one c ... gave a predominating growth of Pfeiffer's bacillus. Haemolytic streptococci predominated in the ... one patient and were recovered ...

TABLE 7

Epidemics resembling influenza

Results of Cultures from the Chatham epidemic in November

Patient	*Disease.*	*Haemolytic streptococci isolated*	*Per cent of total flora*
B—p	Pharyngitis	0 (throat swab)	
O—r	,,	0 ,, ,,	
B—e	,,	0 ,, ,,	
T—s	,,	0 ,, ,,	
P—n	,,	0 ,, ,,	
B—n		+ ,, ,,	90
L—n	Pharyngitis, mucopurulent exudate	0 ,, ,,	
G—n	Follicular tonsillitis	+ ,, ,,	1
R—n	Coryza, tonsillitis with follicular exudate	0 ,, ,,	
M—n	Pharyngitis, laryngitis	0 ,, ,,	
S—n	,,	0 ,, ,,	
D—n	Pharyngitis, basal bronchitis	0 (throat swab)	
I—n	Coryza, basal bronchitis	0 (throat swab and sputum)	
M—n	Pharyngitis, laryngitis, basal bronchitis	0 ,, ,, ,,	
P—s	Bronchopneumonia	+ (sputum)	90
,,	,,	+ (empyema pus)	100
S—h	Relapse with follicular tonsillitis	+ (throat swab)	90

4.—Discussion

As in the case of the previous epidemics, the causal organism was not discovered. There was some evidence that the haemolytic streptococcus was concerned both primarily and second... xact rôle of th... inical eviden... milar to the... aetiology fr... on both upp... The disease more catarrh... in nature than epidemic influenza and there is a

more marked laryngitis and tracheitis. Further the fauces show more inflammation of the tonsils, frequently with exudate, so that confusion arises with follicular tonsillitis of streptococcal origin. This confusion is made more pronounced by the simultaneous occurrence in the epidemic of cases with definite infection with haemolytic streptococci. If spread of infection to the lower respiratory tract occurs, the picture produced is one of catarrhal bronchitis or frank bronchopneumonia Pneumococcal lobar pneumonia has no special relation to the epidemic

D.—The Epidemic at Rugby School, November, 1936

An epidemic of coryza and pharyngitis occurred at Rugby School in November, 1936 There were 30 to 40 cases from a total of 600 boys and the disease was considered by Dr R E Smith to be typical, though mild, influenza such as has been described by him (1936). Gargling from 2 early cases did not yield influenza virus, while cultures of throat swabs from 10 other cases yielded the ordinary flora of the fauces with haemolytic streptococci in small numbers in only one instance Symptoms were slight and comprised sore throat, coryza, sneezing and headache Lassitude and malaise were both slight, one patient complained of abdominal pain, but vomiting, shivering and muscular pains did not occur There was no cough or epistaxis. Pyrexia to 99° or 101° F for one or two days was usually pr

with swel

was seen.

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SECTION II

CLINICAL STUDIES ON THE INFLUENZA EPIDEMIC OF 1936–7

By C. H. Stuart-Harris, D. K. M. Chalmers and E. G. H. Cowen

medical officers in charge of the patients, in order that the natural

1936, and also at the Household Cavalry Hospital, Windsor. By January 1st, 1937, these epidemics had abated and a large outbreak had developed at Chatham where patients were studied in the Royal Naval Hospital The Chatham epidemic waned after a fortnight and study was continued in the Military Hospital at Shorncliffe, minor recrudescences being observed at Chatham and also at Uxbridge in February The object of studying the epidemic in a number of areas was twofold. firstly, to observe as many cases as possible during the limited period of time of an epidemic and secondly, to avoid error in the delineation of the clinical picture because of variations in the severity of the epidemic in different localities.

A.—Epidemiological Data

In each area where the epidemic was studied differences were observed in the occurrence and incidence of the disease. Owing to Christmas leave during or prior to the epidemic and to the entry of recruits in certain of the areas, there was little opportunity for the study of the epidemic in a closed population. However at Shorncliffe an epidemic occurred among the Royal Berkshire Regiment at

vaccination experiment (see Section VII) was performed during the progress of the epidemic and also the population was less stable. The incidence rate for the Berkshire regiment was 14 per cent. and for the Dragoons 9 per cent. The chart shows the occurrence of an isolated case in each epidemic a few days before the main wave, although neither epidemic showed a marked peak in the daily incidence rate The epidemic among the Royal Horse Guards at

Windsor was modified by Christmas leave and a vaccination experiment was also performed there. Chart 4 shows the straggling nature of the epidemic with very low total incidence (9 4 per cent. including cases of coryza) and entire absence of peak At Windsor a number of heavy colds had occurred in early December, suggesting

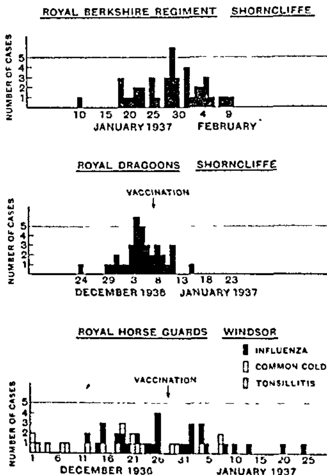


Chart 4

which might conceivably have been due to influenza infection

At Uxbridge the population is floating, there being 2,000 to 3 000 men constantly in the depôt, with an entry of 200 recruits per week

and a transference of a corresponding number from the depôt each week. During November the daily sick parade increased in number owing to the occurrence of a number of cases of coryza and pharyngitis, including some febrile patients. On December 11th cases of a different type began to appear and in these patients a diagnosis of influenza was made and confirmed by recovery of virus. Febrile cases of influenza continued to occur at the rate of 5 or 6 per day until December 23rd when the depôt emptied After Christmas a large number of afebrile patients reported sick and a very few febrile cases continued to occur until February, when there was a minor recrudescence with typical influenza among new entries to the depôt and virus was again recovered. The recrudescence soon died down, however, and was replaced by frank tonsillitis.

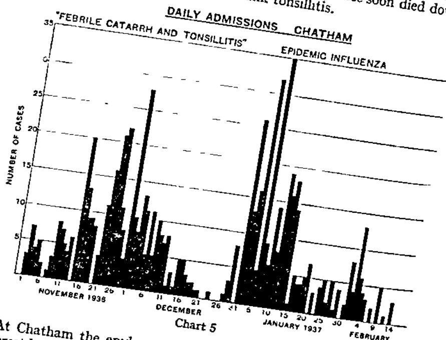


Chart 5

At Chatham the epidemic in the Naval Barracks was of special interest because of the previous epidemic in November and December, described in Section I, which proved to be different both clinically and from the point of view of recovery of virus Chart 5 shows the contrast between the two epidemics in the daily admission rate to hospital. There was a considerable gap between the two epidemics, covering the period of Christmas leave, and the influenza outbreak began shortly after the return of men to the barracks. Two main peaks were seen in January in the first and second week, and the second of these was due to the reassembly of the Mechanical Training Establishment on January 6th with the spread of the epidemic here a week later than in the rest of the barracks. A minor recrudescence was seen in February again among new entries to the barracks,

including a number of Canadian naval ratings visiting the port. It is impossible to give accurate figures of total incidence at Chatham, but including all patients treated in barracks there were not more than 400 cases during January and February out of a population of 4,000. The daily admission rate to hospital shows a higher peak in January than in November, and the peak was also reached more rapidly in January. Tonsillitis was common in November and December and then disappeared until March.

To summarize the experience in the various areas, the first point was the low total incidence in each area, 14 per cent. being the highest rate.

Secondly, the incidence of the disease among various groups of individuals in the epidemic areas, revealed certain interesting facts. Ninety per cent. of the 120 patients studied in detail were aged 15 to 24, 70 per cent. being under 20, but it was impossible to obtain accurate information of the age distribution of the population from which the patients came, owing to the rapidly changing personnel in some of the epidemic areas. Table 8 shows the incidence of influenza and of all minor respiratory infections (colds, tonsillitis and influenza) for certain groups in the Nore Command from which the patients at Chatham were drawn. The figures relate to the period between January and March, 1937. It is seen that the incidence of influenza upon recruits of less than 12 months' service in the Royal Naval barracks was 3 to 4 times that upon trained men in the same barracks who belonged to the same age group of 18 to 20 approximately. The incidence for the boy seamen of less than nine months' naval service was the highest of all groups (26.7 per cent.) and was more than twice that for the artificer apprentices, many of whom had served for two, three or four years. Boy seamen and artificer apprentices were both aged 15 to 20. The factor of duration of stay in the service which is connected with the rate of change of the population is therefore of great importance in determining the incidence of infection by influenza virus, as suggested by Dudley (1926). Within the narrow limits of age studied, the importance of age in determining the incidence of the disease was overshadowed by the factor of duration of residence in the infected population.

TABLE 8

Incidence of minor respiratory infections in the Nore Command (Shore Establishments), January to March, 1937

Group	Incidence per cent. Influenza	Incidence per cent. Total minor respiratory infections	Average strength of group
Royal Naval Barracks recruits	12.7	28.2	1 440
Royal Naval Barracks trained men	3.8	5.6	5 711
Boy seamen	26.7	41.8	2 053
Artificer apprentices	12.9	21.8	818
[illegible]			

Thirdly, there was some variation in the clinical severity of the epidemic in the various areas At Uxbridge the first wave produced a high proportion of severely ill patients many of whom had bronchiolitis, although there was only one patient with true pneumonia; yet in the February recrudescence the cases of influenza were much milder, although there were three cases of bronchopneumonia. The other epidemics were all milder than the first wave at Uxbridge, with many apyrexial cases at Chatham and a lower proportion of cases with bronchiolitis. Table 9 shows the geographical distribution of 120 patients who have been studied in detail, and a sub-division has been made into patients with simple influenza, patients with influenza and bronchiolitis, and patients with pneumonia. The incidence of pneumonia was very low in each area, the number of cases in the table giving a distorted picture of this because of deliberate inclusion of severely ill patients for observation. The pneumonia cases at Shorncliffe were mostly post-influenzal pneumonia developing days or weeks after the original attack of influenza. The mortality rate was very low, with no deaths at Uxbridge, and none at Chatham from the naval barracks, although two men died in the hospital from pneumonia, one a soldier, and one a sailor from a ship. One man died at Windsor with septicaemia following frank tonsillitis which did not appear to be influenzal in nature. Another died at Shorncliffe from suppurative sinusitis and intracranial complications following an attack of influenza. None of the fatal cases was studied in detail.

TABLE 9

Geographical distribution of 120 *cases*

	Uxbridge	*Chatham*	*Windsor.*	*Shorncliffe.*
Influenza	20	44	7	15
Influenza with bronchiolitis	8	7	0	2
Pneumonia	2	8	0	7
	30	59	7	24

Finally, the incidence of previous respiratory infection in relation to the type of disease seen in the individual patients is shown in Table 10 Thirty-six (30 per cent.) of the 120 patients studied in detail had had "influenza" before, 16 (13 per cent.) had had tonsillitis, and most had suffered from colds—43 (35 per cent.) frequently Lower respiratory tract infections include bronchitis (11), pleurisy (3), pneumonia (5), bronchitis and asthma (1). Sub-

TABLE 10

Previous respiratory infections in 120 cases

	Influenza	*Tonsillitis*	*Colds*	*Bronchitis*	*Pleurisy*	*Pneumonia*	*Asthma*
Influenza	28	11	31	6	2	4	1
Influenza with bronchiolitis	6	2	8	2	1	1	0
Pneumonia	2	3	4	3	0	0	0
Total	36	16	43	11	3	5	1
Per cent	30	13	35	9	2	4	0 8

Previous lower respiratory tract disease in patients with influenza = 13 = 15 p c.
Previous lower respiratory tract disease in patients with influenza and bronchiolitis = 4 = 23 p c
Previous lower respiratory tract disease in patients with pneumonia = 3 = 17 p c.

B.—Clinical Data

The patients who were studied in detail may be described under three headings —

1 Simple influenza (86 patients)
2 Influenza with "bronchiolitis" (17 patients)
3 Pneumonia (17 patients)

In the description which follows an attempt will be made whenever possible to relate the clinical findings to the evidence obtained as to the presence or absence of influenza virus infection. Ideally, every patient described clinically should have been tested for virus infection by inoculation of garglings or sputum into ferrets, but practically this was not possible because of the numbers of ferrets, but practically have been required Patients of similar clinical type were, therefore, grouped together and selected individuals from the groups were tested for virus The detailed results on the recovery of virus will be found after the clinical description in the section on pathological investigations and the results of serological investigations will be described in the separate section dealing with this subject

I—Simple Influenza

(a) *General Description*

The epidemic consisted for the most part of cases of a short febrile illness varying in severity, but nevertheless presenting a remarkably uniform picture on the whole

(i) *The typical picture*

The picture which was typical of the disease amongst men in the services was as follows After feeling perfectly well in the morning, the patient was seized with headache felt ill and began to shiver in the afternoon He passed a restless night waking at intervals with headache and aching in the limbs or back, and developed a short dry cough The next morning there was pyrexia, the temperature continuing to rise during the day and reaching 102° or 103° F.

TABLE II

Percentage frequency of symptoms in 84 patients with simple influenza

Symptoms at onset.	*Per cent*	*Symptoms during the whole fever.*	*Per cent*
Headache	54	Malaise	91
Shivering	39	Headache	87
Muscular pains	21	Anorexia	77
Cough	20	Shivering	74
Malaise	18	Coryza or nasal obstruction	73
Coryza	15	Cough	71
Insomnia	14	Dizziness	62
Sore throat	11	Muscular pains	51
Dizziness	11	Sore throat	43
Vomiting	6	Ocular symptoms (photophobia or pain on movement of eyes)	33
Fainting	2	Insomnia	32
Abdominal pain	1	Sweating	31
Sweating	1	Expectoration	31
		Pain in the chest	24
		Epistaxis	21
		Constipation	21
		Nausea	21
		Vomiting	11
		Dyspnoea	11
		Abdominal pain	8
		Hoarseness of the voice	6
		Fainting	4
		Faint feeling	2

(ii) *The Symptoms*

The relative frequency of the various symptoms as they occurred throughout the entire course of the illness is set out in Table II, but it is convenient to describe the symptoms which were general or constitutional, separately from those arising locally from the respiratory tract

General S[illegible]

[illegible]

ill[illegible]

ex[illegible]

cor[illegible] in their environment during the whole course of the fever After admission the degree of malaise bore a close relation to the presence or absence of pyrexia, and once the temperature was normal the patient felt perfectly well

Headache —Headache was persistent for the first 24 hours of illness except in those patients receiving analgesics It was severe and continued beyond this time in a few patients, while in those with intermittent pyrexia it usually reappeared when the temperature rose above normal. The situation was frontal except in two patients who complained of occipital aching. A few patients who denied headache complained of a " heavy feeling in the head "

Anorexia —Appetite was poor or absent during the fever, returning with the fall of temperature A few patients felt hungry even when pyrexial Distaste for food was naturally most marked in patients complaining of nausea or who had vomited

Shivering —" Feeling cold and then shivering " was the description of this symptom by a number of patients No patient shivered after admission in a manner suggesting a rigor The fact that this symptom was present so frequently (74 per cent) is perhaps correlated with the extremely rapid rise of temperature at the onset of the fever

Dizziness.—Dizziness yet not vertigo was a common feeling before admission and was noticed during the fever on getting out of bed and standing upright.

Muscular pains.—Aching pains in the muscles and occasionally stiffness of the shoulders were noted in only half the patients and were rarely severe. [illegible]

commonly.

Ocular symptoms.—Photophobia occurred in 18 patients, and in another 13 pain on movement of the ocular muscles was noted, both symptoms occurring in 3 patients. A diffuse aching behind the eyes was also an occasional complaint.

Insomnia.—A restless night was a common symptom before admission to hospital, the restlessness being sometimes caused by coughing or by aching, but in any case, after admission, little difficulty in sleeping was noticed.

Sweating.—A number of patients complained of sweating before admission to hospital and on the first examination 19 were found to be sweating. Yet except for the sweating accompanying the fall of temperature at the end of the fever, especially if a diaphoretic had been administered, this symptom was neither troublesome nor obvious.

Abdominal symptoms.—Anorexia has already been described. Nausea was mentioned by 18 patients and vomiting occurred in 11. Because of the general opinion that influenza may sometimes manifest itself in a gastro-intestinal form, the symptoms of involvement of the alimentary canal need special mention. Vomiting was a symptom before admission to hospital in 9 patients, the number of times varying from one to twelve; in 2 other patients vomiting occurred after admission—one without and one with previous sickness. On the whole therefore if vomiting occurred it did so [illegible]

had vomited twelve times before admission but who did not vomit once he was put to bed. He had other symptoms typical of influenza including [illegible]

continued after admission and there was a high temperature for two days (103°–104° F.). There was no cough, the signs in the respiratory tract were not proportional to the degree of fever, and virus was not recovered from the gargling of this patient. However, the patient was in contact with other proved cases of influenza and without the test for virus would have been accepted as a case of gastro-intestinal influenza. This patient was the only one seen in the epidemic who had diarrhoea; no bacteriological investigation [illegible]

Fainting.—Fainting occurred twice as the first symptom of illness but, together with other symptoms in the first 24 hours of the disease, it occurred in two other patients. A faint feeling without loss of consciousness also occurred twice. Those patients with fainting had genuine loss of consciousness as was shown by the head injuries mentioned above in the discussion of the onset of the disease. No test for virus was made on any patient who fainted at the onset of the illness but a good rise in influenzal antibody content of the serum developed in one such patient during the illness.

Respiratory Symptoms

Coryza and nasal obstruction —A nasal discharge, sneezing and a blocked nose comprised the nasal symptoms. Coryza, meaning actual nasal discharge, was observed in 20 patients after admission. Nasal obstruction, usually partial but sufficient to give a nasal twang to the voice, was present in 48 patients, of whom 8 had coryza as well. The degree of coryza was rarely more than a slight "snivel" and was considerably less than that occurring in a common cold. Sneezing was not observed after admission.

Epistaxis —Epistaxis had occurred in 8 patients before admission, including two from whom virus was recovered, and 3 of these together with another 10 had nose-bleeding during the fever. It was profuse and repeated in a few patients, and in one or two other patients not considered to have epistaxis, blood-streaked mucus was blown from the nose.

Cough —Cough was present in most patients, being definite in 60 (71 per cent), while a further 13 admitted that "a slight cough" was present. Yet of the whole group only about 8 patients had a really troublesome and barking cough. This was very obvious on going into the influenza wards which were quiet in the daytime but rather more noisy in the evening, with occasional coughs. One medical officer expressed the position succinctly by saying that about 4 patients in a ward of 30 would be doing most of the coughing. Cough was more constant towards the end of the fever than at the beginning, and was usually the last symptom to disappear during convalescence. Its intensity was, moreover, related to the presence of abnormal signs in the chest, except in 2 patients who are described in the notes as having a marked cough without abnormal chest signs, these perhaps had a tracheitis.

Expectoration was noted in the history of 21 patients (25 per cent), while 26 patients (31 per cent) produced sputum after admission. The usual sputum was of a light green or yellow-green colour, consisting of small pellets or discrete nummules of mucopus. A little blood-streaking was seen in the sputum from one patient. Sputum was small in amount except in two patients who produced several ounces on one or two days. The presence of expectoration was always related to the presence of abnormal signs in the chest.

Sore throat —In spite of the fact that only three patients had normal fauces throughout the fever, many showing striking abnormalities, a complaint of soreness was made in only 36 instances (43 per cent). In 32 of these the sore throat was present on admission and speedily disappeared, and in 4 it appeared for the first time on the 3rd or 4th day. Dryness of the throat was on the other hand noted more commonly.

Pain in the chest —Pain in the chest was either a substernal soreness or a tight feeling across the front of the chest, it was present in only 20 patients (24 per cent) and was severe in but a few instances. The infrequency of this symptom, which may be considered to represent a tracheitis, together with the infrequent occurrence of a persistent cough can only mean that a tracheitis was not a dominant feature of the epidemic.

Hoarseness of the voice —Only 5 patients either had on admission or developed later a definitely hoarse voice, although huskiness was common. Aphonia did not occur in the group of patients under discussion, but was seen in two patients at Uxbridge who appeared to have mild influenza. Laryngitis was not severe in degree in the majority of patients therefore.

Dyspnoea —Ten patients said that they were a little short of breath on exertion before reaching hospital, and 1 patient had true dyspnoea after admission. In the latter, however, the dyspnoea was due to bronchial spasm, the patient having suffered from chronic bronchitis and asthma for some years.

(iii) *The fever*

Duration —The average duration of the fever varied slightly in the different areas investigated, as did the severity of the disease. As the greatest number of cases occurred at Chatham, the temperature charts of a large number of cases were inspected, and from these

the average duration of fever after admission to hospital was calculated The patients in this larger series were given routine treatment with aspirin on admission but not again unless this was necessitated by symptoms There were 215 patients and the average duration of the fever was 2 6 days Among the patients specially studied and excluding those receiving special therapy and those with complications, the average duration of fever for 69 patients was 3·6 days If we subdivide the group according to locality the following result is obtained :—

Chatham, 35 patients, minimum of treatment, average 3·2 days of fever.

Windsor, 6 patients, salicin therapy, average 3·3 days of fever.

Shorncliffe, 11 patients, sodium salicylate therapy, average 3·4 days of fever.

Uxbridge, 17 patients, aspirin and citrate therapy, average 4·4 days of fever

Between the large treated group at Chatham and the ones specially studied and receiving practically no treatment, there was a difference of half-a-day of fever on the average This is probably due to unconscious selection of patients for study, and it would appear that the description of the disease as a 3-day fever, or a 4-day fever from the onset of symptoms, is justified Five or more days of fever were seen in 17 out of the 69 patients (24 per cent) Separation of the age-groups was made among [illegible] ficant difference was revealed, th[illegible] years being 3 6 days, for 20-24, 3 [illegible] 3 4. Separation of those with a [illegible] failed to reveal any difference, both groups having an average of 3 6 days of fever.

Height of the pyrexia—Among the 69 patients, the temperature peak at the height of the fever was 104° F in 1 patient, 103° in 14, 102° in 27, 101° in 19 and 100° or less in 8 It has already been stated that at Chatham one apyrexial patient was admitted to every 6 patients with fever From no apyrexial patient however was virus actually isolated Calculation of the average highest temperature and sub-division according to locality also suggested that Uxbridge had rather more severely ill patients, for the average here was 102 1° F, and in the remaining areas the average did not reach 102°.

Type of fever—A great variation was seen in the shape of the individual temperature charts and, inasmuch as this variation was present amongst the untreated cases of the series, it cannot be the result of therapy Among a total group of 286 febrile patients consisting of the original 69 plus 217 others from Chatham, no fewer than 50 (17 4 per cent) had one day of fever only, and a further 66 had a steadily diminishing fever Continued fever was present in 6 apart from these, and the remaining 164 showed an intermittent or remittent fever with prominent spiking Amongst these there were 66 (23 per cent of the whole) which seemed of special interest and which showed a chart with two dominant peaks and a much

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from the onset of symptoms, is justified Five or more days of fever were seen in 17 out of the 69 patients (24 per cent) Separation of the age-groups was made among the selected patients but no significant difference was revealed, the average for the group 15–19 years being 3 6 days, for 20–24, 3 5, and for the small group over 24, 3 4 Separation of those with a past history of "influenza" also failed to reveal any difference, both groups having an average of 3 6 days of fever.

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lower or normal temperature in between (the saddle-back curve of *Dudley, 1918). The interest of this type of fever lies in the fact that* it resembles the type of fever seen in ferrets experimentally infected with influenza virus. In these animals the fever has been described as diphasic, but a letter M or merely a two-peaked curve conveys the

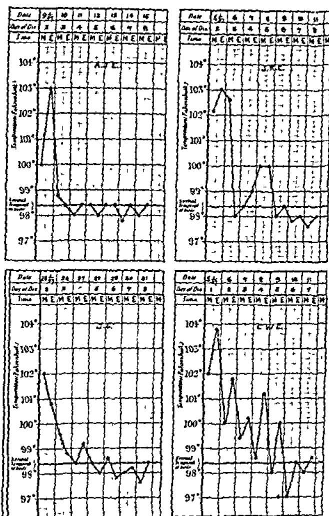


Chart 6.

shape of the temperature chart. In patients showing this fever the temperature might fall to normal for two readings in between the two peaks, and symptoms were usually in abeyance at this time. The curve is not a diagnostic feature of the disease but might aid diagnosis in a group of patients among whom about one in five might be expected to show this "signature" of influenza virus infection. Chart 6 shows the commonest varieties of fever and J.R C shows

the diphasic curve Chart 7 shows human and ferret fevers side-by-side for comparison. Influenza virus was recovered from patients whose fevers in turn resembled all the different types figured in Chart 6

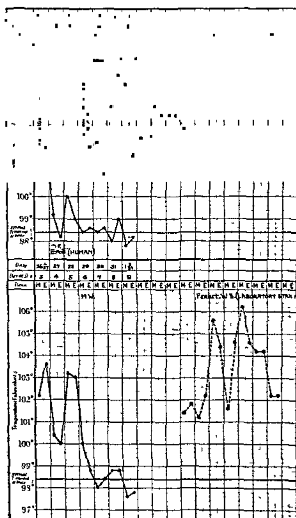


Chart 7

Pulse and respiration rate—Contrary to expectation a relative bradycardia was not seen frequently although this has been stated to be a characteristic of epidemic influenza (French, 1920; Jordan,

chest suggesting that the condition was influenzal. Seven patients had nasopharyngeal mucopus which was a dried deposit on the pharyngeal wall in two.

Fifthly, there was disproportion between physical signs and symptoms.

Cervical glands.—No case of true cervical adenitis occurred. The tonsillar glands were palpable in 31 patients though their size was never great, and they were not tender

fir
be

one or more days In 2 patients of this series rates below 50 were recorded, one being 48, and the other 42 for two days Subsequently a slight degree of tachycardia (90–100) developed in a few patients An electro-cardiogram of one patient during this tachycardia showed sinus rhythm without any abnormality In no patient was any abnormality of the heart detected on clinical examination.

Chest—Those patients with very marked and persistent abnormal physical signs in the chest, have been separated from the group of simple influenza and are considered under influenza with "bronchiolitis." Amongst the cases of simple influenza there were abnormal physical signs in the chest in

patients had a patch of râles and rhonchi usually at the base on two or more days, while one patient who had suffered from asthma in the past had general bronchial spasm for several days So far the physical signs described were consistent with a small or large tube bronchitis, but in the remaining 11 patients signs which could not be so interpreted were elicited These consisted of a combination of weak breath sounds occurring in scattered patches with slight impairment of percussion note over these, and fine or medium râles Such signs were almost invariably basal or axillary in position and the change

small in amount consisting of pellets or nummules of light green mucopus, and only one patient produced a moderate quantity of sputum, while one other produced sputum streaked with blood

Radiograms were taken in 4 patients, in two with indefinite physical signs at the lung bases, and in two with suppressed breathing and râles at the bases No X-ray abnormalities were demonstrated.

A combination of bronchiolitis and atelectasis with or without oedema would therefore appear to be the best explanation of the physical signs in these patients but further discussion on the interpretation of the physical

Abdomen—No abnormality was observed in the abdomen.

Reflexes—The tendon reflexes were examined in 67 patients, were normal

not reveal any abnormal constituents

(v) *Complications*

Relapses—Relapses of fever associated with chest disease have been described in 3 patients from 2 of which influenza virus had been recovered in the initial illness Six other patients developed relapses, in 1 with otitis media, and in 5 with tonsillitis Three of the patients with tonsillitis developed this as an intercurrent infection, being part of an epidemic of intercurrent tonsillitis occurring in one ward. The remaining two were readmitted with follicular tonsillitis Throat swabs examined from two of the 5 patients with tonsillitis showed haemolytic streptococci in almost pure culture One patient with secondary tonsillitis developed otitis media, while one had had, and continued to have throughout, signs of bronchiolitis at the bases of the lungs. Garglings from 3 patients during relapses associated with chest signs and tonsillitis respectively were tested on ferrets but virus was not recovered

Quinsy developed on the 4th day after an attack of typical influenza in one patient.

Herpes labialis developed in two patients on the 3rd day of the disease, and influenza virus had been recovered from one of these prior to the onset of the herpes

Sinusitis—There was tenderness over the frontal sinuses associated with pain in 2 patients Neither developed suppuration One patient, not included in the detailed series but seen at Shorncliffe, developed suppurative sinusitis apparently involving the sphenoid sinuses on the 8th day after influenza, and eventually died from intracranial complications The remaining patients had neither symptoms nor signs of sinus involvement, but special methods of examination of the sinuses were not employed On the other hand, in at least one of the epidemic areas, numerous cases of suppurative sinusitis occurred as a late sequela some six to eight weeks after the influenza infection

The relative paucity of complications other than those associated with chest disease in this epidemic agrees with the experience in the June epidemic of 1918 (French, 1920), and with the epidemic in September, 1918, in the United States as described by Bloomfield and Harrop (1919) The lack of evidence of sinusitis, in particular, was impressive because this complication was expected to occur frequently

(vi) *Convalescence*

There is little to describe with regard to convalescence Most patients recovered strength extremely rapidly once they were afebrile and there were no complaints of mental depression. This

latter symptom seemed indeed to be more usual during the height of the fever when the mentality was dull and lethargic, although no patients actually complained of depression. Patients with fever for more than 4 days took longer to recover and felt weak when they first got up. Slow pulse-rates (50-60) occurred during the first few days of convalescence in 19 patients and 2 further patients had pulse-rates of 42 and 48 on the 5th and 6th days of illness after the pyrexia had ceased. Although convalescence seemed rapid, both men and boys appeared pale and ill for some

hat convalescence is protracted after an attack of influenza. On the other hand the lack of complaint of lassitude or of mental depression may be attributed to the particular population under study, and in civil life these symptoms may be more frequent French (1920) noted that convalescence was rapid in the influenza

valescence was usually rapid and mental depression was practically never seen, except in cases with prolonged fever and bronchitis. Leichtenstern, however, described in 1905 a long and tedious convalescence accompanied by mental depression in even mild attacks of influenza and this view would appear to be current at the present time.

(c) *Illustrative cases of proved influenza virus infection*

Case 3 Influenza 5 days fever No Chest signs. W.J.B, aged 21, was quite well until 8 p m on the 7th February, when he had a headache, felt shivery and ached about the waist and slightly in the back There was slight coryza and cough but no sore throat or expectoration He slept well On the 8th he felt poorly, was still aching and had a headache his appetite was poor and his bowels did not act There was still cough The eyes ached on movement On admission the temperature was 101° F and rose to 103 6° in the evening The patient was very flushed with slight cyanosis of the lips The eyes were slightly suffused, the nose appeared normal and the tongue was coated with dense white fur The throat showed

abdomen was natural and the reflexes were normal

On the 9th the temperature had fallen sharply to 99·8° F., the pulse being 86 Vomiting had occurred during the night but the patient felt better and had no headache or aching in the muscles The nose felt slightly blocked and the throat remained

was less facial flush On

and there was renewed h

quite well but nose still slightly obstructed and slight cough Appetite good The temperature rose to 100° F in the evening and the pulse rose to 88 No signs in the chest February 15th Convalescent Felt a little weak on getting up and still slight cough No abnormal signs on examination except for a slightly granular appearance of the posterior pharyngeal wall

Summary —A case with five days of fever, pharyngeal signs but no abnormality of the chest Acute onset Virus was recovered from garglings collected on the 2nd day of illness

Case 4 —Influenza 1 day fever Indefinite chest signs —A J E, aged 16 Quite well until January 9th at 6 p m when he felt ill, sneezed and found his nose clogged He slept poorly and had a sore throat and shivered January 10th—still poorly, headache, blocked nose and sore throat Slight cough but no sputum No muscular pains Appetite poor. Slightly short of breath on exertion On admission the temperature was 100° F rising to 103°, and the pulse 102 rising to 116 There was a general facial flush on forehead, cheeks and nose, and a slightly bloated appearance. The lips were slightly cyanosed The eyes had a heavy appearance, being

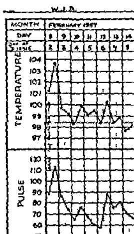


Chart 8

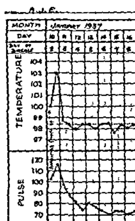


Chart 9

droopy, and a little suffused The nose was blocked The tongue was moist and clean The throat was flushed, with injected vessels and a rather mottled [illegible] of the posterior pharyngeal wall The voice was nasal The [illegible] There was occasional cough and the breath [illegible] few râles were heard [illegible] The abdomen was normal Reflexes [illegible] ongested veins with normal discs The urine showed no [illegible]

January 11th Feeling quite well except for slight cough Temperature normal A little sputum consisting of small pellets of greenish mucopus The throat was drier mottled and very injected The chest showed an occasional râle at the right base January 12th Well and good appetite, Herpes labialis January 13th Still slight cough Marked herpes on the philtrum of the upper lip Throat moister, with a granular appearance and map-like injection of the vessels The chest showed an occasional added sound at both bases and there was still a little sputum Convalescent No bradycardia

Summary —One-day fever Herpes labialis Virus was recovered from garglings collected on the 2nd day of illness

Case 5.—Influenza Relapse. Basal chest signs.—E.A.O., aged 17. Was quite well until January 1st when he developed a headache. January 2nd,
d felt ill
There
nere was
... symptoms continued and the patient was admitted on January 4th. The temperature was then 101° F. rising to 102°, the pulse remaining at 80–84. On examination the patient was strikingly flushed on cheeks and nose, and to a less ext...
cyanosed. The eyes were water...
normal. The tongue was clean.
a slightly granular pharyngeal wall. The voice was normal. There were showers of fine râles at the base of the right chest and slightly weaker breath sounds here.

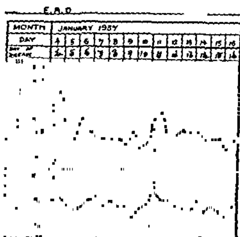


Chart 10.

January 5th. Temperature fell sharply to normal. There was slight stiffness of the neck on waking, but the patient felt much better, having no headache. There was a loose cough and a small quantity of mucoid sputum. The throat appeared much the same and the signs in the chest persisted. January 6th. Well, apart from cough. The temperature rose to 100° F. in the evening. January 7th. Profuse epistaxis. Still cough and slight sputum. The throat was moist and had a finely granular aspect. The chest showed weak breath sounds at both bases with an occasional râle at the left base and ...

was no bradycardia.

Summary.—A case with insidious onset, 4 days of fever, and a relapse on the 11th day. Initial fever of diphasic type with two dominating spikes. Bradycardia.

Pharyngeal signs, epistaxis, basal signs in the chest.

Virus was recovered from garglings collected on the 4th day of illness, but not on the 11th day during relapse.

2—Influenza with "Bronchiolitis"

(a) *General Description*

In a small proportion of the patients with influenza seen during the epidemic, physical signs were elicited in the chest which suggested that there was an extension of the inflammatory process beyond the bronchi. In some of these patients, now to be described, the signs were so extensive or persistent that the condition of the chest dominated the clinical picture Yet there was no doubt that the infection was, at any rate, initially influenza, for virus was recovered from each of five patients whose garglings or sputa were tested on ferrets. These cases have been termed influenza with "bronchi-

evidence of clinical and radiological examination that the process involves the alveoli as well as the bronchioles, although whether by atelectasis, oedema, or by actual consolidation is undecided

There were 17 patients from the original group of 120, who have been included in this group There was no sharp clinical distinction from the patients previously described under straightforward influenza, the differences being a greater degree of general illness and extensive or persistent abnormal signs in the chest Retrospectively, there appear to have been two different types of the condition In one, the patient was admitted with symptoms and signs of influenza suggesting a severe attack, abnormal physical signs appeared in the chest within a day or so, persisted for a variable length of time, and then disappeared In the other, the patient had what appeared to be a typical and not necessarily severe attack of influenza, recovered and then underwent one or more relapses of fever Physical signs in the chest might or might not have been discovered during the initial fever but, in any case, they became apparent during the relapses and were often more extensive and persistent than the degree of pyrexia indicated Influenza virus might be recovered from the throat during the initial fever, but could not be recovered later during the relapse

Two illustrative cases will now be described and then the symptomatology and physical signs, and finally the significance of the condition will be discussed.

(b) *Illustrative Cases*

Case 6 —Influenza with "bronchiolitis" during the acute illness —A W D A , aged 19, was taken suddenly ill with headache, dizziness and shivering and was admitted to hospital on December 13th The temperature was 101 6° F , the pulse rate 88 and the respiration rate normal The patient was flushed and slightly cyanosed with an injected throat On December 14th there was sore throat blocking of the nose and slight cough with a continuance of the pyrexia On December 15th, the patient was still feeling ill and had a dry cough The face was very flushed with a dusky hue, the lips were cyanosed and the general aspect was typical of influenza with drooping eyelids, glistening conjunctivae and a dull mentality. The fauces were

glistening and injected, with some nasopharyngeal mucopus. The nose wa obstructed and the voice normal. Rhonchi were heard at both bases wit [illegible]

brighter, but slight dusky flush and definite cyanosis. Cough and sputum continued. The percussion note was slightly impaired over the right lowe lobe and here the breath sounds were suppressed with râles of a peculia sticky nature. The blood-pressure was 114/70. There was no albuminuria.

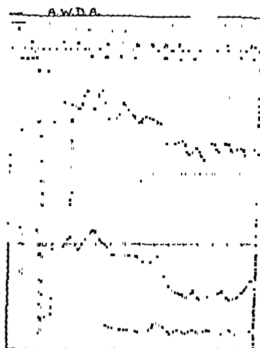


Chart 11.

The temperature fell to normal on December 20th but physical signs continued to be present in the chest for another 5 days with cough and sputum during this time. On December 31st the patient was convalescent with no
cou[illegible]
cha[illegible]
nor[illegible]
21st [illegible]
44, [illegible]
gra[illegible]
sho[illegible]
On December 26th the pulse rate began to rise and the pulse improved in volume and became more regular in rhythm. During convalescence the mentality was strikingly different from that during the fever and the patient gained strength remarkably rapidly.

Case 7.—Influenza with "bronchiolitis" of relapsing type.—R. N. T., aged 17, was taken ill suddenly with headache, shivering and cough on January 5th. The temperature was 101·2° F., the pulse rate 88 and the respiration rate normal. There was a dusky facial flush, slight cyanosis of the lips, and

glistening, slightly suffused conjunctivae The fauces were dry and injected, the nose was stuffy with slight coryza, and there were no abnormal signs in the chest January 6th There was still headache, and slight cough A

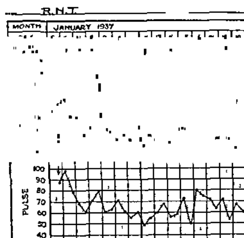


Chart 12

purulent sputum Again râles were heard at both bases, while on the 18th

that a small dose of concentrated antiviral horse serum was given intravenously *on January 5th but without obvious effect (see serum treatment, p 82)*

These two patients whose histories are described above, were tested for the presence of influenza virus, and virus was recovered from garglings collected on the 2nd and 1st day respectively Neither patient had had any previous disease of the respiratory tract

(c) *Detailed Description*

(i) *Symptoms*

There were few essential differences between the symptoms in this group of patients and those of simple influenza Preliminary coryza preceded the illness in three patients, and the onset of the

illness was sudden in 8 only, out of the 17. The onset was heralded by the occurrence of headache, cough, shivering, malaise or muscular pains, in this order of frequency. During the fever the only differences noted in the symptoms were the increased severity of the feeling and appearance of illness, a greater complaint of sore throat (in 81 per cent. of patients) and a predominance of cough and expectoration over all other symptoms after the first few days. Pain in the chest occurred in 8 patients, being substernal, or a tight sensation in 5 patients, xiphisternal in 2 and situated in the side in 2. Sweating, often profuse in degree, accompanied the fall of temperature and was particularly striking in 4 patients.

[illegible]
wi [illegible]
ba [illegible]
productive one. Sputum varied in character, being frothy, green or yellow-green in colour and mucopurulent in type. It was abundant in several patients and frankly purulent in three. Bloodstreaking occurred once only. A nummular sputum or else one occurring in fine pellets, was seen more often in the relapsing type than in the other.

(ii) The fever

In the group with bronchiolitis in the first phase of the illness (9 cases), a remittent fever was the commonest, lasting from 4 to 13 days, or for 7 days on the average. In 3 patients the temperature chart was of the type described above as diphasic, showing two dominant spikes. In the second group of 8 patients, a relapsing pyrexia was seen, the initial illness being accompanied by a diphasic type of fever in 4. Occasional spikes of pyrexia might occur up to four weeks from the onset and the temperature returned to normal after periods varying from 11 to 29 days. Three patients showed a sharp relapse on the 7th, 9th, and 10th days respectively, from the onset, with a rise of temperature to between 102° and 104° F., having been afebrile for 4 or 5 days after the initial influenza. In one of these patients the spike of fever was associated with an acute tonsillitis, the patient developing later signs in the chest of bronchiolitis and pleurisy; in the remainder, there were no signs other than those in the chest to account for the fever. The late relapses were not associated with high pyrexia but rather with a "grumbling" type of fever, the temperature being between 99° and 100° F.

(iii) The physical signs

In appearance the patients with signs of bronchiolitis early in the disease did not differ from those suffering from typical influenza. They appeared toxic and ill, with pronounced facial flush and cyanosis. Conjunctival signs as already described were observed. The nose was frequently obstructed, the tongue constantly furred, and the fauces abnormal, with the same injection, swelling

of adenoid tissue, and granularity of the pharyngeal wall. The only patient showing faucial exudate was the patient mentioned above who had a patch of white exudate on the tonsil for one day in the first relapse Cervical adenitis was not seen; the voice was husky not hoarse; there was no sinusitis and only one patient had otitis media accompanying the illness, in this case, from the beginning

Some of the patients in the relapsing group were not seen until the relapse, but those who were observed from the beginning did not differ in general appearance from patients with simple influenza During the relapses, there was, however, cyanosis persisting for many days, without facial flush.

The pulse rate was raised during the pyrexia in both groups of patients; some 30 per cent. showed a relative bradycardia. No abnormalities of the heart were observed in the acute stage. During convalescence 6 patients showed bradycardia with a pulse rate below [illegible]

pulse rate averaging 90, while the temperature was 102° to 103° F. No abnormality was found in the tracing The blood-pressure was usually slightly raised during the initial fever and fell slightly in convalescence

The respiration rate was raised, but not above 30, in 4 patients. Dyspnoea was noted twice, in the presence of extensive signs in the chest, and was most noticeable after the minor exertion of sitting-up in bed

The mentality was dull and apathetic in two patients, the reflexes were normal or slightly diminished Albuminuria did not occur.

The abnormal physical signs in the chest were basal, in all cases except one in which the abnormalities were present at both bases and apices, one base was often more affected than the other Diminution of movement, impairment of percussion note, weak or suppressed breath sounds in patches, fine or medium râles and scattered rhonchi constituted the signs The added sounds were often of a peculiarly sticky or glutinous nature The first abnormal sign to develop was usually a rhonchus or a patch of weak breath sounds and from this the full syndrome would develop There was never bronchial breathing or bronchophony, the voice sounds being usually faint or slightly aegophonic in character

Two patients developed signs of pleurisy In the one, these were present on the 9th day from onset, in a patient who was not seen until this day, but who had been febrile throughout There was friction followed by dullness and weak breath sounds, but aspiration was not performed The other patient had had a mild but typical attack of influenza, virus having been recovered from garglings collected on the 2nd day of the disease On the 9th day, there was a sharp relapse with general symptoms and the development of acute

tonsillitis. Garglings were again taken but virus was not recovered Culture of a throat swab gave less than 1 per cent. of haemolytic streptococci with no preponderance of Pfeiffer's bacillus Physical signs in the chest had been indefinite hitherto, with an occasional rhonchus and weak breath sounds at the bases However, suppressed breathing, an impaired percussion note and a few râles were noted from now on and expectoration of mucopurulent sputum commenced. On the 17th day, there was acute pain in the left side and pleural friction was heard, while two days later the signs suggested a small pleural effusion. Aspiration was not performed and physical signs steadily diminished in degree although sputum continued for a further two weeks, being abundant on some days, and the temperature did not settle until the 29th day from the onset.

The patient with apical and basal signs had initially dullness over both lower lobes, weak breath sounds and fine crepitations The sputum was purulent and the general condition toxic with dyspnoea on slight exertion Râles then developed at the bases, the percussion note became impaired at the right apex with fine râles here also Fever continued for 13 days in all and physical signs were still extensive on the 19th day of the disease, after which they cleared

One patient had extensive signs of acute bronchitis during the first two days of a severe attack of influenza, and then developed an impaired percussion note with weak breath sounds and an occasional crepitation over the right lower lobe. Resolution was rapid, the chest being normal by the 9th day. He had suffered from attacks of bronchitis several times before.

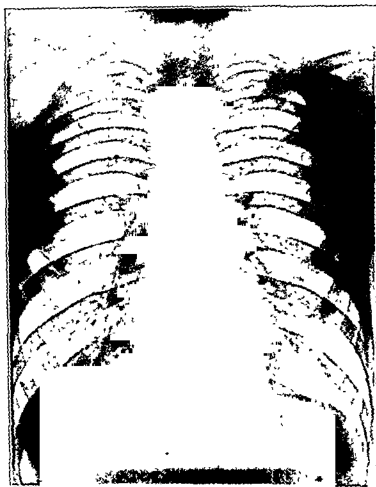
Radiograms were taken on 8 patients and in 4 no definite abnormality was demonstrated although physical signs had been elicited In 4 cases an increase in basal shadows was demonstrated with fluffy shadows which cleared during convalescence. Plate 1 shows the appearance of the chest in one patient during the fever and Plate 2 the same patient 18 days later showing that partial but not complete clearing of the bases had then occurred. Plate 3 shows the chest in one patient who had signs of pleurisy on the

of opacity On the whole, however, far less abnormality was demonstrated in the radiograms of these patients than was expected from the physical examination

(d) *Discussion*

The first point which arises in connection with this group of patients is whether the physical signs in the chest developed because of the lighting-up of previous chest disease by the influenza, or

To face page 56



Influenza with "bronchiolitis"—relapsing type. Day 15. Physical signs at both bases. Febrile

tonsillitis. Garglings were again taken but virus was not recovered. Culture of a *throat swab gave less than 1 per cent. of haemolytic* streptococci with no preponderance of Pfeiffer's bacillus. Physical signs in the chest had been indefinite hitherto, with an occasional rhonchus and weak breath sounds at the bases. However, suppressed breathing, an impaired percussion note and a few râles were noted from now on and expectoration of mucopurulent sputum commenced On the 17th day, there was acute pain in the left side and pleural friction was heard, while two days later the signs suggested a small pleural effusion. Aspiration was not performed and physical signs steadily diminished in degree although sputum continued for a further two weeks, being abundant on some days, and the temperature did not settle until the 29th day from the onset.

The patient with apical and basal signs had initially dullness over both lower lobes, weak breath sounds and fine crepitations. The [illegible] spnoea [illegible] ussion [illegible] e also [illegible] e still extensive on the 19th day of the disease, after which they cleared slowly An electrocardiogram was taken on this patient during the height of the fever when the pulse rate was relatively slow (see above), but no abnormality was found.

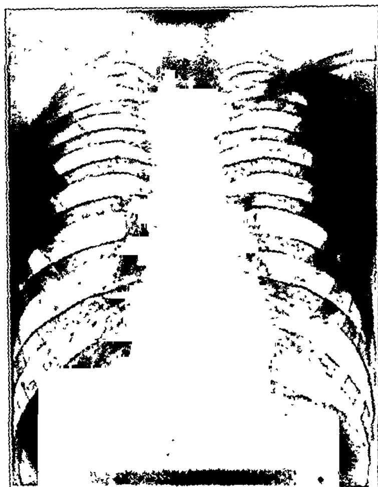
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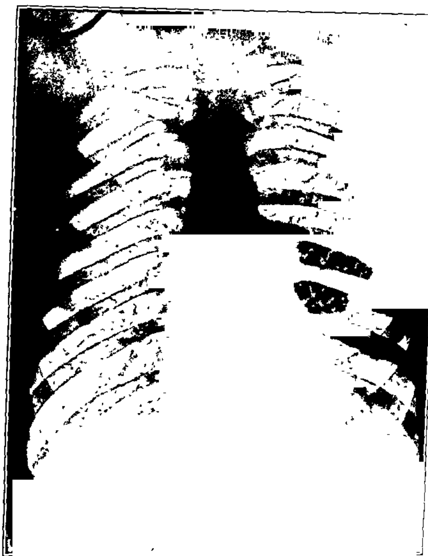
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To face page 56



Influenza with "bronchiolitis"—relapsing type Day 15 Physical signs at both bases Febrile



Same case as Plate 3 Day 35 No abnormal signs in the chest. Convalescent

whether they were the result of the influenza primarily. It is of importance, therefore, to examine the past histories of these patients with regard to previous disease of the respiratory tract. Among those with bronchiolitis during the first four days of the influenza there was only one who had had any previous chest disease, and this was the patient described above, who had had bronchitis in the past and who developed acute bronchitis as well as bronchiolitis. The remainder had had no illnesses with the exception of measles or whooping-cough in childhood, and all had passed a medical examination on entering the Services, a short time before the epidemic. Among the group with relapsing bronchiolitis one patient had had bronchitis, one had had pneumonia in infancy, and the third had had pleurisy a year before the present illness. There appear, therefore, to have been four patients in all in whom the influenza might have caused a lighting-up of previous chest disease. But in these the picture of the chest disease during the influenza differed in only one instance from that seen in those without previous chest disease. This one example was the patient with acute bronchitis as well as bronchiolitis. Finally, the three patients who were most ill had had no previous chest disease of any kind. Therefore, it seems likely that the particular clinical picture under discussion is not due to an infection conditioned by previous disease, but is rather a characteristic of the infection itself, namely, influenza.

Secondly, the possibility has to be considered that the relapsing type of bronchiolitis may be different aetiologically from the bronchiolitis accompanying influenza from the onset. This does not appear to be likely, for few patients of the relapsing type of case had normal chests during the initial influenza. In one or two, however, the initial illness was mild and the relapse so acute that it appeared that the relation of the two processes was rather that one initiated the other, than that they were both induced by the same agent. The fact that influenza virus was only isolated from garglings during the initial illness was also in favour of this and would suggest that the influenzal infection had paved the way for a secondary infection which latter gave rise to the chest condition. Apart from these few patients, however, the long-continued signs in the chest seen in the relapsing type of case could be explained by a slow repair of an inflammatory process induced by the initial influenza. Combining the two pictures, there would be initially an attack of influenza accompanied by an inflammatory process in the bronchioles and followed by slow repair. During the latter stage, secondary infections might occur, leading to a prolongation of the process.

The question of the interpretation of the physical signs in the chest, and the nature of the morbid process will be considered in the general discussion below.

3.—PNEUMONIA

There remain to be discussed those patients who developed signs of definite consolidation of the lung. The group is by far the most

difficult to analyse because of the individual variations, further, the evidence from the pathological side of the importance of the various agents in the causation of the pneumonia has been difficult to interpret. The two patients seen by us, from whom influenza virus was recovered will be described first and an attempt will then be made to analyse the remaining patients.

(a) *Illustrative Cases*

Case 8 —This patient was seen in the Hammersmith Hospital on January 4th and permission to refer to the case has been given by Professor Fraser, and the Chief Medical Officer of the L C C.

N O, aged 16, was quite well until January 2nd, although she had had an attack of rheumatic fever in 1932, and her mother had chronic pulmonary

the heart sounds was present, the blood-pressure was [illegible] sounds were weak on both sides of the chest and front with coarse rhonchi The right base was dull on percussion with distant bronchial breathing The left base had an area of dullness near the apex of the lower lobe, with bronchial breathing

Death occurred six hours after admission From a portion of the lung obtained at post-mortem, influenza virus was recovered, culture of the lung emulsion giving a pure growth of *Staphylococcus aureus*.

This was the only patient seen by us during the epidemic who presented a rapidly fatal course, but at least three other cases are known to have occurred in two other London hospitals and from

seen so commonly in 1918.

December

December 14th

2/84.

influenza virus not recovered)

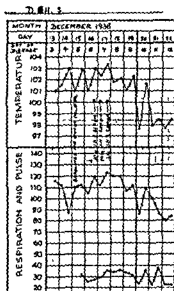


Chart 13

December 19th Much better with lower temperature, less respiratory

sounds but no crepitations Convalescence continued and was uneventful.

inf
in
inv

with a pseudo-crisis on the 9th day The chart shows that small intramuscular doses of concentrated antiviral horse serum were given on the 6th and 7th day, but without any obvious effects (see serum treatment, p. 82)

(b) *Detailed Description of the remaining Patients with Pneumonia*

The remaining patients formed a heterogeneous group amongst which certain clinical types could be differentiated. They may be described under four headings :—

(i) " Typical " influenzal pneumonia.
(ii) Abortive pneumonia.
(iii) Post-influenzal pneumonia.
(iv) Miscellaneous group

Table 13 shows the list of the patients together with data on the pathological investigations.

(i) " *Typical* " *influenzal pneumonia*

Case 9 is an example of what is meant by this term and three other patients were seen, two in military hospitals, and one at Hammersmith Hospital who presented a similar picture. In each case, the onset occurred suddenly with symptoms suggesting influenza—headache, shivering, muscular pains and cough. After a day or two expectoration commenced and physical signs in the chest were elicited. Chest pain was usually present but was not of the type associated with pleurisy at this stage of the disease. The general aspect resembled

was high, the pulse rate raised and the respiration rate was between 30 and 40. Dyspnoea was not marked in spite of the raised rate of respiration and the extensive signs in the chest. One patient was mildly delirious. The appearance of the eyes, blocking of the nose, injection of the fauces and huskiness of the voice all agreed with the signs in simple influenza The signs in the chest varied from those discussed under bronchiolitis up to complete lobar consolidation The percussion note was impaired at first and later very dull ; the breath sounds were suppressed, faintly or even frankly bronchial , the voice sounds were reduced, faintly aegophonic or bronchophonic ; added sounds consisted of rhonchi scattered throughout the chest, with sticky râles and fine crepitations over the consolidated area These signs were basal in three patients, basal and apical in one, and both sides of the chest were involved A radiogram in one patient showed well-marked opacity of the lower lobe of one lung and a faint veiling at the opposite base

After a prolonged bout of fever with increasing distress, cyanosis becoming livid or heliotrope, and increasing expectoration, the temperature fell on about the 10th to the 14th day either by crisis

TABLE 13

Table of cases of pneumonia

Patient	Type of illness	Recovery of virus	Influenzal serum antibodies		Culture of sputum			
			Febrile	Convalescent	Pneumo	H influenzae	Staph aur	Haem strep
N O	Fulminating pneumonia (died)	+ (lung) 3rd day	—	—	0	0	+ (lung)	0
D H S	Influenzal pneumonia, pleurisy	+ 5th day	S/125	S–5 × S*	+	+	0	0
E P	„ „ (died)	0 10th „	—	—	+	0	0	0
N W M	„ „ empyema	— —	—	>S	—	—	+ (pus)	—
R C F	„ „ pleurisy	?0 3rd day	—	S/5–S	0	+	+	0
A G W	Abortive pneumonia	0 3rd day	S/125	S	+	+	0	0
J A C	„ „	— —	—	—	—	—	—	—
C M	„ „	?0 4th day	—	S/5–S	0	+	+	+
J T	„ „	0 5th „	—	S/25–S/5	+	0	0	0
A M	Postinfluenzal pneumonia, pleurisy	— —	—	>S	+	+	0	0
C W	„ „ „	— —	—	—	—	—	—	—
R A	„ „ „	— —	S	S	+	+	0	0
W W	„ „ „	— —	—	—	+	0	0	0
W.F	„ „ „	— —	—	S/5	+	+	0	0
S S	„ „ „	— —	—	—	—	—	—	—
J F	Purulent bronchopneumonia ?bronchiectasis	0 2nd day	<S/125	S/5				
P W W I			—	5 × S	+	+	—	0
H D	Influenzal pneumonia ?septicaemia	— —	—	—	—	—	0	—
J M	Bronchopneumonia	0 8th day	—	—	0	+	0	++
	T B bronchopneumonia	0 3rd „	S/25–S/125	>S	0	0	+	+

* S refers to standard anti-influenzal horse serum (III_3).

or lysis. The patient was now well except for cough and sputum, and signs in the chest cleared slowly. Pleurisy developed in three patients with an effusion in two; an empyema yielding *Staphylococcus aureus* on culture developed in one patient. One patient died on the 11th day of illness.

As will be seen from Table 13, garglings and sputum were collected on the 3rd, and the 10th day respectively from two patients and inoculated into ferrets. Virus was not recovered from either specimen, although it was recovered from Case 9 who resembled clinically the other patients in this group. Culture of the sputum gave *H. influenzae* and *Staphylococcus aureus*, pneumococcus (Group IV) and *H. influenzae* and pneumococcus (Group IV) in the three patients.

(ii) *Abortive pneumonia*

There was a group of four patients who had what appeared to be an abortive
influenza.
shivering, r
was that of a patient with influenza, but either on admission or on the 3rd day, physical signs of consolidation of the lung appeared However, by the 3rd, 6th and 7th day in three respective patients, the illness terminated abruptly, while in the fourth a severe shock following intravenous serum therapy was associated with termination of the disease on the 6th day. The physical signs in the chests of these patients consisted of dullness and bronchial breathing in the interscapular region in one on the 2nd day of the disease, scattered rhonchi and doubtful signs at the right apex in another on the 4th day, râles and rhonchi at one base, and dullness, bronchial breathing and crepitations at the other base on the 4th and 5th day respectively in the last two Radiograms showed faint veiling in the mid-zone of the first patient, marked opacity of the right upper lobe of the second, and dense opacity of the right lower lobe only in the third; the fourth was not X-rayed The sputum in these patients was faintly blood-tinged initially in two and contained green mucopus in the others. Attempts were made to recover virus on the 3rd, 4th and 5th days respectively in three patients but none was successful. Culture of the sputum showed in the three patients (i) pneumococcus (Group IV) and *H influenzae*, (ii) pneumococcus and (iii) a mixture of *H influenzae* and *Staphylococcus albus* and *aureus*.

(iii) *Post-influenzal pneumonia*

The next group comprises six patients who had an attack of influenza, recovered and were quite well for a variable period of time and then relapsed suddenly with an attack of pneumonia It is fortunate that in three instances the patient was in hospital during the influenza and though not seen by the author, notes and temperature charts were available for study. Unfortunately no test for virus was made during the influenza but there do not appear to be any grounds for regarding the illness as other than typical and mild influenza.

The history of one of the patients in brief was as follows :—

pleural friction at the right base and dullness at the left base Radiogram showed dense opacity of the left base suggesting fluid January 31st Some irregular pyrexia, cough, mucopurulent sputum Paracentesis of the left chest did not yield fluid

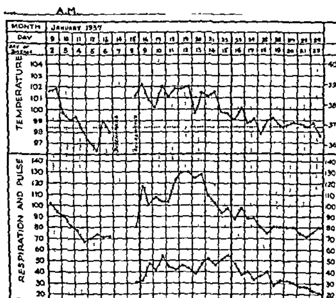


Chart 14

From now on the patient appeared to improve until March 3rd when there was a sharp relapse with more extensive dullness at the left base, a radiogram

The remaining patients may be briefly tabulated —

(1) Apical consolidation began 4 days after an attack of typical influenza in a man about to be discharged from hospital Typical course of lobar pneumonia with crisis on the 7th day

(2) Bilateral consolidation, accompanied by pleurisy at the left base with sterile effusion, commenced in a patient 10 days after mild influenza during

which he was ambulatory. Course was typical of lobar pneumonia. Lysis began on the 6th day.

(3) Consolidation and dry pleurisy at the right base developed in a man 12 days after typical mild influenza. The pleurisy dom... picture but a radiogram showed ...

the initial illness or th... day of the pneu... while conv... content as b... in the pneu... in 4 patient... pneumococcus predominated in all (Group IV in two instances), while *H. influenzae* accompanied the cocci in three instances.

(iv) *Miscellaneous*

Four patients ... to have been ... with apparen... prolonged and relapsing course. ... lung bases, which underwent a morning cough and sputum for some time, and although this was not proved, bronchiectasis was suspected as a condition existing before admission Test for virus on the 2nd day of the disease was negative and the sputum yielded pneumococcus and *H. influenzae* on culture

Then ...

cen... uenza when convales- left ... consolidation in the ... on the 11th day and the temperature became strikingly intermittent, rising from 100° to 105° F daily. Septicaemia was suspected but not proved, and after 5 days the temperature fell to a lower level and convalescence set in slowly without any fresh signs developing The third patient developed bronchopneumonia a week after a cold He had no symptoms suggesting influenza but cases of influenza virus infection were occurring in the depôt at the time he was taken ill He was gravely ill with signs of patchy consolidation of the bases, and developed a left-sided sterile pleural effusion Sputum and garglings were tested for virus on the 6th day of the disease, and virus was not ... of the ...

... 17 ... with fever, headache, ... and cough On the 2nd day of the disease there were well-marked signs of consolidation in the upper part of the right lower lobe and a dense X-ray opacity in this region The general appearance suggested influenza but virus was not recovered from garglings taken on the 3rd day of the disease The signs in the

chest persisted in a relatively unchanged state with low fever and cough Sputum did not appear till the 11th day, and was then mucous becoming mucopurulent On the 30th day, the signs suggested cavitation, and bronchiectasis was suspected. However, tubercle bacilli were found in the sputum and the condition appears to have been an atypical tuberculous pneumonia involving part of the lower lobe The apices were clear by radiological and clinical examination and the tuberculous process was atypical. The possibility of a coincident influenzal infection at the onset appeared likely, but this was not proved However, serum taken during the initial fever had no antibody to influenza virus while that taken 3 weeks later had a good antibody content suggesting that virus infection had occurred

(c) *Discussion*

At least 3 groups of patients with signs of consolidation of the lung could be distinguished during the epidemic These were the fulminating, the influenzal and the post-influenzal pneumonias The fulminating cases appeared to be merely extreme examples of the influenzal type of pneumonia, from which they differed only in having an extremely rapid course The influenzal pneumonias included some abortive and ill-defined cases, but the more typical cases were clinically different from the types of bronchopneumonia and lobar pneumonia which are endemic in this country and occur unrelated to an influenza epidemic Thus the general aspect of the patient with influenzal pneumonia was that of a case of influenza; there were nasal and faucial signs and symptoms; dyspnoea was not noticeable in spite of a raised respiration rate, the signs in the chest approximated to those described as being due to "broncho-

respiratory catarrh was absent with lack of coryza or pharyngitis, the fever often ended by crisis, the signs in the chest were those of lobar consolidation and radiograms invariably showed dense opacity, the sputum was often rusty and viscid The only difference from classical pneumococcal pneumonia was absence of dyspnoea, although this occurred when pleurisy developed

At the present time clinical differentiation cannot be carried further than this and far more study will be necessary before these

deliberately selected for study and the actual case-incidence of pneumonia was low

C.—Pathological Investigation

1.—Recovery of Influenza Virus

Table 14 shows the results of the attempts to recover virus from garglings of the patients described above. From simple cases of influenza there were 10 successful, one doubtful, and two unsuccessful attempts. The ferret-positive cases were clinically representative of the group described above and analysis of their signs and symptoms separately from the others revealed no significant differences. The negative cases were also typical clinically The two afebrile cases were negative as were all the relapses and the gastro-intestinal case, but one case with gastric onset yielded virus. Influenza with " bronchiolitis " gave 5 positives out of 5 tested. The results in cases of pneumonia have already been described in the clinical section, virus having been obtained from two cases.

TABLE 14

Recovery of virus from patients studied clinically

Clinical picture	*Day of illness*	*Positive result.*	*Negative result.*
Simple influenza	1st	2	0
	2nd	6	2 1 doubtful
	3rd	1	0
	4th	1	0
Afebrile " influenza "	2nd	0	1
	3rd	0	1
Influenza with gastric onset	2nd	1	0
Gastro-intestinal " influenza "	2nd	0	1
Influenza with " bronchiolitis "	1st	1	0
	2nd	3	0
	3rd	1	0
Relapse with bronchiolitis	11th	0	1
,, ,, tonsillitis and bronchiolitis	9th	0	1
,, ,, tonsillitis and otitis media	14th	0	1
Pneumonia—			
(i) Fulminating	3rd	1 (lung)	0
(ii) Influenzal	3rd	0	1
,,	5th	1	0
,,	10th	0	1
(iii) Abortive	3rd	0	1
	4th	0	1
	5th	0	1
(iv) Purulent bronchopneumonia	2nd	0	1
Bronchopneumonia	4th	0	1
Tuberculous	3rd	0	1
Total . 35		18	16 Negative 1 Doubtful

On the whole, the positive cases, which are of vital importance for this investigation, were well scattered amongst the groups of patients studied in the various areas, it can be stated with confidence,

therefore, that clinical description has been based upon groups of patients amongst which some, who were typical of the group, were tested and found to carry influenzal virus in the throat. Fuller details concerning recovery of virus from these and other cases are contained in Section IV, p 97.

2.—Examination of Sera for Antibodies

A detailed description of the results of this investigation will be found in Section V, p 115 See also Table 13, p. 61.

3.—Bacteriological Investigations

No elaborate investigations were made, but, whenever possible, throat swabs were cultivated on 5 per cent. blood trypsin agar in order to detect haemolytic streptococci In all, 44 throat swabs were examined, and by a similar method, 17 sputa. The results are shown in Table 15, where the percentages of the colonies of haemolytic streptococci, when present, among the total flora is included. It is seen that haemolytic streptococci were not isolated from simple cases of influenza as a rule and that when present they did not predominate in the flora They were, however, obtained in preponderance from the throats of two patients admitted during the epidemic with a severe sloughing type of exudative tonsillitis, and from two patients with relapses due to follicular tonsillitis One case of relapse with bronchiolitis and one of acute rheumatism gave a small proportion of colonies of haemolytic streptococci.

TABLE 15

Results of throat swab cultures during the influenza epidemic

Type of disease	*No of specimens*	*Number of positive cultures*			
		Haemolytic streptococci		*Pneumococci.*	*H influenzae.*
			Number of colonies		
Simple influenza ..	31	2	Less than 1 p c	7	14
Influenza with "bronchiolitis"—					
Swabs	5	0		0	3
Sputa	4	0		3	4
Pneumonia—Sputa	13	1	90 p c	10	9
Relapse with follicular tonsillitis	2	2	90 p c	—	—
" bronchiolitis	3	1	1 p c	—	—
Admitted with exudative tonsillitis	2	2	75 p c. and 90 p c	—	—
" " acute rheumatism	1	1	5 p c	—	—

The data so far as pneumococcus and *H influenzae* are concerned are open to the criticism that the medium used was one designed for the purpose of isolating haemolytic streptococci. Nevertheless,

from some plates, *H. influenzae* (morphologically) was isolated, sometimes as the predominating organism. The cases of pneumonia from which cultures were made include the various groups of influenzal, abortive and post-influenzal pneumonia, and pneumococci preponderated in the sputum, being frequently accompanied by *H. influenzae*. The haemolytic streptococcus was the predominating organism in one case of bronchopneumonia. The cases of influenza with bronchiolitis usually had *H. influenzae* in the sputum and occasionally pneumococcus but the latter predominated in the flora in one instance only.

The chief importance of this part of the investigation lay in the fact that during previous epidemics which had been investigated and did not yield influenza virus the haemolytic streptococcus had been encountered with some frequency in the throat flora. As will be seen from reference to the description of these epidemics above, cases of frank tonsillitis from which haemolytic streptococci could be isolated in almost pure culture, were frequently encountered as an integral part of this variety of epidemic. In the influenza epidemic, however, tonsillitis of this type was rarely encountered; the two patients admitted with exudative tonsillitis were the only ones seen amongst some hundreds of patients in the various hospitals (excepting the cases occurring during a ward epidemic at Chatham).

4.—Erythrocyte Sedimentation Rate

Sedimentation rates were estimated on 12 patients at Chatham by the laboratory technicians using a modified Westergren technique. Table 16 shows the results, which were not considered abnormal amongst the patients with influenza. The patient with acute rheumatism is included for the sake of comparison.

TABLE 16

Estimation of sedimentation rate in patients during the influenza epidemic

Patient.	*Disease.*	*Day of disease*	*Febrile or not*	*Sedimentation rate (fall in mm. in 1 hour)*
J F B	Simple influenza	3rd	No	5
R. D S M.	" "	4th	Yes	5
L D.	" "	5th	Yes	9
N S W	" " .. .	5th	No	12
R. F S	" "	5th	Yes	3
A. J E .	" "	5th	No	2
D B .	Bronchiolitis	4th	Yes	6
E A O .	"	13th (relapse)	No	10
B F H .	"	14th (relapse)	No	8
J A. C ..	Abortive pneumonia . ..	3rd	Yes	28
F C. S .	Follicular tonsillitis . ..	8th (relapse).	Yes	16
T. M. C	Acute rheumatism	12th	Yes	124

5.—*Blood Counts*

The leucocyte count has been formerly regarded as a useful diagnostic aid in influenza and it was for this reason that leucocyte counts were carried out on patients during the various epidemics described above. At the beginning of the influenza epidemic a number of leucocyte counts were made by one of us, the results of

diagnostic leucopenia was found A more elaborate investigation was therefore undertaken by Mr D L Hughes, whose results appear below. Confirmation of the early results was obtained, and it would appear, therefore, that the leucocyte count is not of use in the diagnosis of epidemic influenza, unless the experience in this epidemic was exceptional

D.—Epidemic among the Nursing Staff at Hammersmith Hospital

A small epidemic occurred among the nursing staff at Hammersmith Hospital from December 27th, 1936, to January 9th, 1937, and there were 12 cases in which the diagnosis of influenza was made, including one case of pneumonia The outbreak coincided with the admission to hospital of a number of cases of influenza from the West London area

Garglings from two nurses on the 2nd and 3rd days of the disease were tested on ferrets and influenza virus was recovered from both specimens. It seemed likely that the epidemic was due to the virus, therefore, and the clinical picture among the nurses was of interest in comparison with that seen in patients in the services. The average age of the twelve nurses was just under 30, which is higher than the average for the soldiers, but the description of the clinical picture by Dr J. G Scadding of the British Postgraduate Medical School agrees closely with that already given for the men and boys in the Services. Substernal soreness was noted more frequently among the nurses, but epistaxis was not seen Abnormalities of the fauces were also less common, but when seen were of the same type as those already described. Abnormal physical signs in the chest were found in only two nurses, including the case of pneumonia, but the general type of illness seems to have been identical with that in patients from the services

Dr Scadding's note is as follows —

"*Symptoms*—The typical onset was characterized by relatively sudden prostration, sometimes with shivery sensations, sufficient to be regarded as a rigor in three instances One nurse continued her work until she fainted on duty Common symptoms at onset were headache (9 cases) and aching pains in the limbs and back (7 cases), headache occurred in all at some time during the course and in only three was no complaint ever made of pains in the limbs or back. Throat symptoms were not prominent at the onset, dryness and discomfort rather than

TABLE 17

Leucocyte counts on influenza patients

Patient	Day of disease	Type of disease	Leucocyte count. Total	Polymorphonuclears.		Lymphocytes		Mononuclears	
			Per c mm	Per cent	Per c mm	Per cent	Per c mm	Per cent	Per c.mm.
J F C	2nd	Simple	9,000	81	7,300	9	800	10	900
P W O	2nd	"	4,600	79	3,600	16	730	5	230
*R M	2nd	"	14,000	79	11,000	12	1,700	9	1,200
"	3rd	"	10,000	69	6,900	25	2,500	6	600
C D	3rd	"	9,800	66	6,470	24	2,350	10	980
P P	2nd	Bronchitis, Bronchiolitis	9,400	59	5 500	22	2,000	17	1,600
*A. W D A	3rd	Bronchiolitis	7,400	70	5,180	26	1,920	4	290
"	4th	"	9,400	74	6,900	21	1,970	4	370
"	5th	"	10,000	76	7,600	20	2,000	4	400
"	7th	"	8,400	75	6,300	19	1,600	6	500
J F S	6th	"	6,400	60	3,840	30	1,920	9	570
B M R	6th	"	9,200	78	7,200	18	1,650	4	360
"	7th	"	6,800	83	5,600	14	930	3	200
*D H S	5th	Pneumonia	16,800	94	15,800	5	840	1	168
"	6th	"	16,800	90	15,100	9	1,510	1	168
"	7th	"	15,000	93	14,000	6	900	1	150
"	9th	"	25,000	97	24,000	2	500	1	250
		Simple and bronchiolitis	4,600–14,000	59–83	3,600–11,000	9–30	730–2,500	3–17	230–1,600

* Virus-positive.

soreness being usual; in some cases, complaint of sore throat was not made until the second or third day and, in five (including one of the virus-positive cases) this symptom never occurred. Eye symptoms—soreness and lachrymation—were present at the onset in half the cases, and came on later in three more, but actual photophobia occurred in only three. A mild coryza was present at the onset in four, it was at its worst on the second or third day, and was then present in seven cases Cough was a common early symptom, appearing by the second day in ten cases. It was frequently accompanied by a painful sensation behind the sternum, varying from slight soreness to quite a severe 'tearing' pain There was usually no sputum at first; later scanty mucopurulent sputum was produced in six. Anorexia was constant from the onset Vomiting occurred on the second day in two cases

In three, there was a history of a slight coryza for a week before the sudden onset of prostration and typical influenzal symptoms

Pyrexia —The total duration of pyrexia varied between one to four days, except in one case in which pneumonic consolidation developed in the left lower lobe on the fifth day, prolonging the pyrexia to the fourteenth day In most cases, including the two virus-positive ones, the administration of salicylates was avoided, lest a characteristic temperature response should be masked; but the charts were of varied type, and no one typical response could be detected

Physical signs —The general aspect at the onset was very constant A generalized flushing of the face appeared to affect especially the ears, and frequently the lips presented an almost cyanosed appearance When this was combined with red, watering, heavy-lidded eyes, a very striking picture was presented The pyrexia was associated with sweating, but this was not excessive, and was rarely the subject of complaint by the patient

The pharynx usually showed a general injection extending over the pillars of the fauces and soft palate No exudate was seen. In five cases, an unusual appearance of the posterior pharyngeal wall was noted, it was dry, rather glistening, and presented prominent lymphoid follicles This appearance was not seen after the third day No cervical glandular enlargement was observed In three cases, nothing abnormal was ever seen in the appearance of the pharynx

No evidence of sinusitis, laryngitis or otitis media was obtained

Pneumonic consolidation of the left lower lobe developed on the fifth day in one case, it was associated with the presence of pneumococcus type II in pure culture in the sputum Apart from this, abnormal physical signs were detected on examination of the chest in one case only In this, on one examination, a

patch of fine râles during inspiration which persisted after cough was found at the right base. Nothing further developed, and the case was otherwise indistinguishable from the rest.

Convalescence.—After the pyrexia subsided, convalescence was usually rapid Cough persisted sometimes for a week or ten days, but was unproductive. No tendency to undue mental depression was observed.

Blood counts.—The blood was examined on the second and the fourth day in seven cases. The total leucocyte count ranged from 3,400 to 7,000, with an average of 5,200 per c.mm. No significant change in the differential count could be found in this small series, and it was impossible to follow the counts during convalescence." (*cf.* Scadding, 1937).

E.—General Discussion

If the clinical events of the 1936–37 epidemic are viewed as a whole, they are seen to have ranged from an extremely mild illness to rapidly fatal cases of pneumonia, while most of the cases were of a short febrile illness accompanied by signs of infection of the upper respiratory tract. In deciding the question as to whether the clinical picture seen in the 1937 epidemic was in any way exceptional, or whether it was a fair representation of influenza epidemics in the past, a fundamental difficulty arises at once. Certain epidemics have been described above where the diagnosis of influenza was made and these epidemics have been shown to be unrelated to influenza virus infection [illegible] of epidemic influenza, such epidemic [illegible] ones, would almost cert[illegible] influenza Thus the literature of influenza epidemics is confusing because many aetiologically different conditions have probably been described in the past under the same title. The fact remains, however, that certain of the great epidemics of the past have resembled clinically that encountered recently. Thus the clinical features of the June wave of influenza in 1918 (French, 1920; Report of the Influenza Committee to the Advisory Board D G.M.S France, 1918), agree well with those described above This holds not only for the epidemic in England but also for that in the United States in 1918 (Jordan, 1927) There would appear to be a definite clinical picture in the epidemics of influenza which sweep through the communities of entire nations, and there is now evidence that these epidemics are associated with the filterable virus pathogenic for ferrets and mice The nature of th[illegible] described by Francis (1937) is still obscure [illegible] in semi-isolated communi[illegible] ure seen in 1937 is less str[illegible] nic occurring at Rugby School described by Smith (1936). The population affected here was young and this may account for the lack of symptoms in the patients, on the other hand streptococcal complications were common The fact that influenza virus could not be

recovered in a similar though milder epidemic at Rugby in 1936 suggests that some of the earlier epidemics were not of virus origin.

On the whole the majority of the cases seen during the 1937 epidemic presented a remarkably uniform picture. Case after case exhibited similar features and the patients differed from each other in severity of illness only On the pathological side, the evidence that the typical case of simple influenza described above is an [illegible]

occur, then an afebrile illness with slight symptoms would form the next grade of severity to such silent infections With regard to variations in the clinical type, an illness with the usual symptoms of influenza but with vomiting at the onset was shown to be of virus aetiology in one case Intestinal types of disease, however, were not seen. Again, the only nervous types of illness seen during the epidemic were in certain of the severely ill patients with chest signs who were drowsy and lethargic Virus was recovered from the throat of one such patient but no definite signs of organic disease in the nervous system were made out

The most important variation in the disease was the occurrence of patients with signs of lung involvement These were not sharply differentiated from the remaining patients in the epidemic. Many of those with the simple disease had abnormal physical signs in the chest, then there were the cases with more definite chest disease called influenza with "bronchiolitis," and finally there were the cases of pneumonia Every grade of chest infection was represented in the epidemic, therefore, and this close grading of chest disease does not seem to have been described in previous accounts in the literature, where pneumonia has been separated from influenza as though the two diseases were separate

The condition of "bronchiolitis" does not seem to have attracted the attention it deserves, some authorities (French, 1920) have regarded the prolonged signs in the chest as being due to a lighting up of previous lung disease, a view which has already been considered above and dismissed as unlikely On the other hand other authorities appear to have described the condition as an influenzal pneumonia, Martin (1919) gave an account of physical signs in the chest very similar to those described above, in his account of the clinical features of pneumonia occurring in influenza Thus he described suppression of the breath sounds in patches which may persist for days even if the temperature is normal He concluded that "save in the cases which resemble frank lobar pneumonia, the physical signs lead to the conclusion that the condition is a diffuse, patchy involvement of both lungs, with considerable oedema, supervening on an invasion of the finer bronchial tubes" Winternitz

et al. (1920) have described changes in the bronchioles of an inflammatory and degenerative nature as an integral part of the lung pathology during the epidemic in November 1918. In the cases described above as influenza with " bronchiolitis " a widespread consolidation of the lung bases was excluded by radiological examination, and indeed there was less abnormality in the radiograms than clinical examination had suggested. The added sounds could best be explained as arising from the finer bronchioles and the suppression of breath sounds was believed to be due to small areas of collapse or of oedematous infiltration of the alveoli around the terminal bronchioles. Such an interpretation of the physical signs agrees with that of Fraser (1918) who described similar signs in the chest in a group of cases of P.U.O. seen at a base hospital in France in 1918 The occurrence of pleurisy in some of our cases was an additional argument in favour of an alveolar involvement rather than of one confined to the bronchial tree. Again there was no clear distinction between the cases of " bronchiolitis " and those of definite pneumonia, where the alveoli were clearly involved. The rôle of the virus in these different types of chest disease has not been fully determined. The cases of influenza with " bronchiolitis " it may be emphasized were all proved to have influenza virus infection by the recovery of virus from the throat during the early stages of the illness.

Less uniform results were obtained in the cases of pneumonia, although virus was obtained from the lungs of three rapidly fatal cases and from the gargings and sputum of a case with extensive consolidation which ended in recovery. In these cases where virus was obtained from the lung, part at least of the morbid process in the lung must have been due to virus infection. Thus the most reasonable interpretation of the virus attack on the lower respiratory tract in man is that the infection can affect the lung in several ways, the mildest resulting in a bronchitis, the next most severe in a bronchiolitis, and finally an alveolitis develops as a result of direct spread from bronchus to bronchiolus and thence to alveolus.

Some support for this view is obtained by a consideration of the behaviour of influenza virus under experimental conditions in ferrets and mice In the mouse, the virus will produce a range of pathological conditions varying from a bronchiolitis to a widespread lobar consolidation, if administered under an anaesthetic (Straub, 1937) In the ferret the virus produces a range of events closely analogous to that described above in man. Thus the typical infection in the ferret with fever, constitutional upset and nasal lesions seems to correspond to the simple case of influenza in man If the inoculation of the freshly-isolated virus in the ferret is carried out under an anaesthetic the virus may attack the lung, and if repeated passage is carried out the virus may then attack the lung when administered intra-nasally alone without anaesthesia Clearly influenza virus is potentially pneumono-tropic in the ferret, and because of this pulmonary lesions would be expected to occur in human beings

infected with virus from time to time In both ferret and mouse, influenza virus is able to produce lung lesions unaided by bacterial attack, but in the infection of pigs by the analogous virus of swine influenza (Shope, 1931) lung lesions are extensive only when the virus is aided by a hae [illegible]
influenzae suis I [illegible]
lesions in man fr [illegible]
attack.

The rôle of the virus in producing a susceptibility of the lower respiratory tract to secondary bacterial attack is seen clearly in the post-influenzal pneumonias Leichtenstern wrote in 1905 "In a large number of cases, the pneumonia follows on an attack of influenza. One, two, or even more days later, a relapse occurs sometimes but not always with a rigor; the influenza manifestations seem to recrudesce, but in reality they are the first signs of the slowly developing pneumonia. Many of the so-called relapses depend upon this condition In these cases the pneumonia attack comes on the first time the influenza convalescent goes out, hence the universal view that the patient convalescing from influenza is very liable to catch cold, and easily gets inflammation of the lungs." These post-influenzal pneumonias are clinically similar to ordinary bacterial pneumonias and have no special relation to influenza. But a combined and simultaneous bacterial and virus attack might have been the cause of the other pneumonias which have been studied and which have been called "influenzal pneumonia." Part of the failure to recover virus from some of the cases of pneumonia which were [illegible]

[illegible] culture from the lungs of each of the three rapidly fatal cases of pneumonia which also yielded virus In the other cases, the pneumococcus was often found in the sputa either alone or more commonly with *Haemophilus influenzae* The haemolytic streptococcus was isolated once only from the sputa, which contrasts with the experience recorded during the November wave of the 1918 epidemic when some authors recovered this organism frequently (Fildes, Baker and Thompson, 1918) Further work will be needed before the exact rôle of virus and bacterium in the production of lung disease in man can be elucidated However, in relation to this problem, the great difference between the case-incidence and mortality from pneumonia during the 1937 epidemic and the November wave of the 1918 epidemic, may be considered This difference could be explained in two ways, either by a difference in the frequency and type of bacteria co-operating with the virus or by a difference in the virus It was surprising that the haemolytic streptococcus failed to establish itself more frequently in the population studied during the 1937 epidemic. Our previous studies had shown that the streptococcus was a common cause of respiratory infections in military depots, and yet there was

less streptococcal disease during the epidemic of influenza than in the previous epidemics which were not due to the virus.

As a result of the experience gained in the combined clinical and pathological study of the influenza epidemic in 1936–37, it may be tentatively concluded that influenza virus infection in man constitutes a clinical entity. Further work will be necessary in a future epidemic and amongst the civil population before this conclusion can be accepted as proved. Meanwhile, however, the delineation of the clinical features of influenza virus infection permits a subdivision of the group of epidemic respiratory disorders which have been labelled "influenza." The failure of the epidemics at Woolwich, Eastchurch, Chatham and Rugby in 1936 to yield evidence of influenza virus infection, renders significant such clinical differences as existed between these epidemics and the influenza epidemic. In the absence of exact knowledge of the aetiological agent or agents in these epidemics resembling influenza but not due to influenza virus, it is not possible to say whether they are all representative of one condition or whether they represent merely a group of allied disorders. On clinical grounds the Woolwich and Chatham (1936) epidemics appeared to resemble each other, but the Eastchurch and Rugby epidemics had individual peculiarities suggesting that they were different from these and from each other. In the next sub-section the possibilities are discussed of differentiating epidemic influenza

separation from epidemic influenza.

F.—The Differential Diagnosis of Epidemic Influenza

The object of this research has been to attempt to correlate the isolation of influenza virus with the clinical picture in the patients from which it can be obtained. It is realized that the experience of only one epidemic is insufficient to justify dogmatic statements regarding the symptomatology and differential diagnosis of influenza.
ifferen-
ticular
attention was paid to the features summarized below.

1.—Epidemic Influenza

(i) *History*.—Onset is sudden without premonitory symptoms The first symptoms are general or constitutional, comprising headache, shivering, muscular pains and dizziness Respiratory symptoms
2nd day
perature

(iii) *General aspect.*—The typical facies is heavy and drowsy with drooping eyelids, glistening eyes, dusky facial flush and slightly cyanosed lips

(iv) *Physical signs* —These are, obstructed nose, furred tongue, husky but not hoarse voice, and signs of pharyngitis The particular characteristics of the pharyngitis are its posterior position, its large-vessel injection, a tendency to dryness, and a granular appearance Signs in the chest comprise rhonchi or a few râles at the bases towards the end of the fever.

(v) *Complications* —Chest complications predominate over all others with a characteristic picture of "bronchiolitis," and a range of pneumonic conditions also characteristic clinically. Pneumococcal complications are common Sinusitis occurs chiefly as a late sequela.

(vi) *Variations.*—On the whole cases are remarkably uniform in clinical appearance and there is no tendency to admixture with other diseases such as tonsillitis The most important variation from the

population is a closed one

2—"FEBRILE CATARRHS"

In contrast with the features described above as characteristic of epidemic influenza, the catarrhal conditions which were studied in the Woolwich and Chatham (November) epidemics showed the following characteristics —

(i) *History* —Onset is insidious with premonitory "cold" and cough for several days Respiratory symptoms usher in the disease and sore throat and cough dominate the picture. Cough is paroxysmal, irritating and painful, with substernal soreness over the trachea. Expectoration varies greatly, being sometimes profuse. Hoarseness of the voice develops

(ii) *Course* —General symptoms of illness are overshadowed at the onset but are present during the fever with headache and muscular pains The fever has no characteristic course and shows no special tendency to be diphasic in type

(iii) *General aspect* —Often that of a patient with a heavy cold, or with brightly flushed face, injected conjunctivae and slightly cyanosed lips

(iv) *Physical signs* —These are, obstructed nose, clean or furred tongue, hoarse voice, and signs of tonsillitis or pharyngitis. The latter consists of involvement of the anterior as well as the posterior part of the fauces, intense capillary injection, and exudation of mucous, mucopurulent or follicular material Signs in the chest are absent usually but rhonchi may be heard

(v) *Complications* —Chest complications are commoner than others and comprise bronchitis of large or small tubes, or broncho-pneumonia. The haemolytic streptococcus is a common incitant of the chest complications

(vi) *Variations.*—The clinical picture varies greatly with alternation of the pharyngo-laryngo-tracheitis syndrome and frank tonsillitis, liable to be confused with follicular streptococcal tonsillitis.

(vii) *Characteristics of epidemic*—Gradual development from the basal respiratory disease of the population (coryza and tonsillitis). Slow rise and fall with prolonged duration of epidemic over several weeks.

The major contrasting points between epidemic influenza and "febrile catarrhs" are set out in Table 18. So far as epidemic

TABLE 18

Differential diagnosis of epidemic influenza and febrile catarrhs

	Epidemic influenza	*Febrile catarrhs*
Onset	Sudden	Insidious
Symptoms	Constitutional symptoms preponderate.	Respiratory symptoms preponderate
Cough	Short and dry	Paroxysmal irritating, painful, often productive
Voice	Husky	Hoarse
Throat	Posterior pharyngitis, no exudate	Tonsillitis as well as pharyngitis; exudate common
Fever	Sometimes diphasic	Rarely diphasic
Complications	Bronchiolitis and pneumonia	Bronchitis or bronchopneumonia
Epidemic	Short with rapid "peaking"	Prolonged and "grumbling"
Contacts	Clinical picture uniform although graded in severity	Clinical picture variable with frank tonsillitis in contacts
Leucocyte count	Not diagnostic	Not diagnostic.
Virus	Influenza virus recoverable from pharynx	Influenza virus not concerned

influenza is concerned, no single symptom or sign is diagnostic, owing to the variation in the clinical picture in individual patients. The first symptoms which are complained of at the onset of illness show [illegible] Chart 15, which is based [illegible] lar appearance of the p[illegible] with a dry matt surface resembling granulation tissue which has never been [illegible]

patients If the full [illegible] the history and signs [illegible] particularly if the patient be vi[illegible] among his immediate contacts, then differential diagnosis of the two conditions is possible It is when a single isolated patient is seen that difficulties arise in the diagnosis and caution should be exercised in making a diagnosis of influenza unless the picture is typical of that described above During a widespread epidemic it should moreover be recognized that many minor variations of the typical picture of influenza are likely to occur

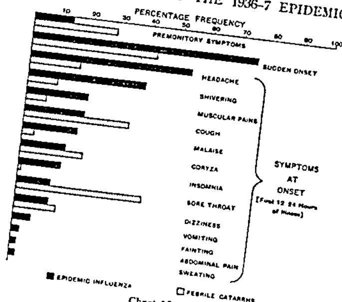


Chart 15

3—Other Conditions Liable to be Confused with Epidemic Influenza

(a) *Simple Coryza and Pharyngitis*

This condition was seen in its purest form during the Rugby School epidemic Confusion with epidemic influenza has arisen in the past from the fact that during an epidemic of influenza many mild and atypical cases occur which can only be described as coryza, "influenzal colds" or pharyngitis Apart from influenza epidemics, however, there is a condition both endemic and epidemic which comprises a feverish "cold" Accompanying the coryza and in some cases overshadowing nasal symptoms there is sore throat, an injected but moist pharynx with prominent lymphoid nodules, and slight pyrexia. General symptoms are never marked and are short-lived There is no real resemblance to the typical case of influenza It is possible that this disease is related to the group of "febrile catarrhs" being a mild example of infection by the same agent or agents On the other hand, it may be related to the common cold and may represent a more severe example than usual of that infection. Whatever the cause of the disease may be, cases of simple coryza and pharyngitis should not be regarded as being influenzal in aetiology, and the use of the word "influenzal" cold should be avoided

(b) *Streptococcal Tonsillitis*

Streptococcal tonsillitis is the second commonest sporadic condition to be diagnosed as influenza It has a sudden onset with considerable

malaise, headache, and muscular pains. There is shivering, a sudden rise of temperature and a sore throat. But *neither nose nor voice* are affected as in influenza and the throat often develops exudate. The only type of exudate which experience has shown to be constantly correlated with the presence of the haemolytic streptococcus, is a white sloughing exudate on both tonsils, the latter structures being swollen and reddened but not ulcerated. Naturally follicular [illegible]

occur in the "febrile catarrhs" but not in epidemic influenza

Streptococcal tonsillitis without faucial exudate is the only variety liable to confusion with epidemic influenza and the chief points of contrast are the soreness of the throat, which is much more painful in streptococcal infection, the capillary injection and moistness of the pharynx and the almost invariable tender enlargement of the cervical glands draining the tonsils in streptococcal infection. The chest usually shows no abnormal signs in streptococcal fever while contacts of the infection show more readily differentiated faucial signs with exudate.

(c) *Lobar (Pneumococcal) Pneumonia*

During the Woolwich epidemic, one patient was deliberately selected for investigation because he showed constitutional rather than respiratory symptoms He had shivering, backache, a dull feeling in the head, cough and a feeling of malaise and the only abnormal physical signs were slight injection of the pharynx and an occasional rhonchus at the right base. Forty-eight hours later there were signs of complete consolidation of the base of the right lower lobe, and there was rusty sputum containing pneumococci in abundance. Thus the case was one of lobar pneumonia, although early symptoms had suggested that the infection was influenzal in nature. Later during the influenza epidemic a similar difficulty arose in distinguishing between influenza and pneumonia. When pneumococci were found in the sputum of a patient with pneumonia, perhaps in pure culture, it was thought that the case was one of ordinary pneumococcal pneumonia occurring during the epidemic. This thesis was at first supported by inability to recover influenza virus from such cases of pneumonia However the only cases of pneumonia [illegible] occal pneumonia [illegible] The remainder resembled cases of influenza from the general aspect and differed in their course from typical cases of pneumococcal pneumonia Finally [illegible] of pneumonia [illegible] izal [illegible] nce [illegible] ing of a widespread epidemic a case symptomatolog[illegible] epidemic influenza may later prove to be a case of lobar pneumonia of pneumococcal origin

(d) Gastroenteritis

The unfortunate use of the term "gastric 'flu" or "gastro-intestinal 'flu" has undoubtedly led to the mis-diagnosis of many cases of gastrointestinal disorder. There is no doubt that vomiting may occur at the onset of epidemic influenza just as it may occur at the onset of any other acute infection. During the one influenza epidemic which has been studied clinically vomiting was occasionally encountered in patients with typical attacks of influenza but intestinal symptoms were very rare. In the future, it is possible that this experience may not be repeated, and it is therefore necessary to be cautious about the existence or otherwise of gastric or intestinal types of influenza. Certainly it is justifiable to recognize the existence of influenza with gastric symptoms at the onset, but in a case of diarrhoea and vomiting, gastroenteritis or other abdominal conditions should be suspected unless there are coincident respiratory symptoms and signs.

(e) Nervous disorders

One or two patients with severe influenza were so stupid mentally and appeared so drowsy that the possibility of an encephalitis was considered. No abnormal physical signs were elicited in the central nervous system, however, and the patients presented respiratory symptoms and signs; the cerebrospinal fluid was not examined. Nevertheless, such manifestations in the nervous system may be responsible for the text-book descriptions of "nervous" forms of influenza. All that can be said at present is that no definite evidence of organic nervous disorder was obtained in the cases of influenza which have been studied in the recent epidemic. In each epidemic area which was visited one or two cases of typical cerebrospinal fever occurred and these did not resemble cases of influenza in any way. Such occurrence of meningococcal infection is not an exclusive characteristic of epidemic influenza, for 7 cases of cerebrospinal fever occurred during the Woolwich epidemic in 1936.

G.—Nomenclature

The word influenza has become a byword in clinical medicine for the description of almost any vague clinical condition exhibiting fever without localizing signs, and its application has, unfortunately, been extended so that it covers conditions other than disorders of the respiratory tract. Thus by the use of labels such as gastro-intestinal and nervous influenza this malady has been claimed to be polymorphic in its manifestations as, for instance, rheumatic fever. Yet a perfectly definite clinical picture has been shown to exist; on the pathological side a virus has been recovered whose specific characters are no longer in doubt. Further other epidemic respiratory disorders hitherto labelled "influenza" which differed clinically from epidemic influenza have yielded no evidence of infection by the specific virus. As evidence accumulates it becomes increasingly probable that epidemic influenza is a specific disease

not only aetiologically but also clinically and therefore conditions which mimic it should be differentiated whenever possible, by some change in nomenclature. The only possible argument for a continuation of the use of the word influenza to describe all epidemic respiratory disorders is the fact that the minor forms of these epidemics may exhibit resemblances. However, no one will deny that chicken-pox and small-pox in their atypical and abortive forms resemble each other clinically, yet the terms are used and accepted as referring to type examples of the diseases which can be readily differentiated.

It is tentatively proposed that the name "epidemic influenza" should be given to the specific virus disease and that of "febrile catarrhs" to the pharyngo-laryngo-tracheitis syndrome The term for the latter disease or diseases may cause controversy but has been chosen to emphasize the catarrhal nature of their manifestations in the respiratory tract, in contrast with the drier inflammation of epidemic influenza.

H.—The Attempted Serum Treatment of Epidemic Influenza

Laidlaw, Smith, Andrewes and Dunkin (1935) have described the use of an antiviral horse serum in the treatment of mice experimentally infected with influenza virus. The serum (IH_2), which was prepared by inoculating a horse with ferret material infected with human influenza virus (W-S) and concentrating the resulting serum 8 times, had neutralizing power against the virus *in vitro*. Given intravenously or intraperitoneally to mice, a dose of 0·25 c c. increased the survival rate and caused a resolution in lung lesions in animals infected previously with influenza virus The serum had some effect even if given 3 days after the virus, but was more effective when given on the 1st or 2nd day after infection had been induced

Five hundred c.c of this concentrated serum were available for clinical trial, and all administrations were supervised or carried out by one of us. Table 19 shows the details of all the patients who were treated No clinical effect was observed in the case of the first two patients, who received small intramuscular doses, but the serum appeared to produce an effect when given intravenously. Chart 16 refers to the third patient A T., who received 75 c.c. of serum intravenously in three doses Each time the serum was given, an immediate effect was observed. The face which was very flushed and appeared swollen, became paler and more normal in appearance within five minutes of the injection of serum and the patient fell asleep. The abnormal facies reappeared 4 hours after the first dose and 20 hours after the second, but not subsequently. The temperature showed no immediate effect, but was normal on the 3rd day after admission, although the general aspect of the patient and the presence of râles and suppressed breathing at the right base, initially suggested a severe infection In this case the serum appeared to have an immediate effect, which resembled a detoxicating action, and possibly led to the early establishment of convalescence. The

remaining six patients were treated along similar lines in order to confirm this result, if possible. It will be seen that 25 c.c. of serum even intravenously failed to shorten the disease in one patient although a transient immediate effect occurred. Fifty c.c. appeared to abort the infection in one patient but failed in another although an immediate general effect was observed in both. Seventy-five or eighty c.c. of serum appeared to benefit each of the patients to whom it was given. Besides the loss of facial flush and a feeling of improvement, the temperature was either normal or lower than usual on the 3rd and 4th days of the disease and abnormal signs in the chest cleared rapidly. The only adverse effects observed were a complaint

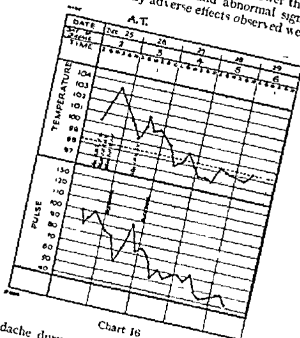


Chart 16

of slight headache during the administration of the serum in two patients, a curious local cyanosis of the skin of both hands in one patient during the injection and delayed serum rashes in two patients.

In order to control the results obtained 10 c.c. of concentrated antistreptococcal horse serum containing the same fraction of serum globulin as the influenzal serum and which was kindly supplied by Dr R A O'Brien, were given intravenously to one patient. Another patient received 50 c.c. intravenously of a concentrated normal horse globulin, also the same fraction as the influenzal serum. No immediate effect was seen in either patient; convalescence was not hastened and delayed serum rashes occurred in both. To establish the clinical impression of the beneficial effect of the influenzal serum

TABLE 19

Attempted serum treatment of influenza

Patient	*Disease*	*Hours after onset*	*Dose*	*Route*	*Immediate effect.*	*Benefit and duration of fever after injection*	*Serum sickness.*
*1 D H S	Influenzal pneumonia ..	6th day 7th "	c c 10 15	Intramuscular "	Nil	3 days No benefit	Nil
*2 J F	Influenzal bronchiolitis ..	15 hours	25	Intramuscular	Nil	5 days No benefit.	Nil.
3 A T	Influenza, chest signs .	18 hours 22 " 42 "	25 25 25	Intravenous "	" Detoxication "	1 day Apparent benefit.	Nil.
*4 C K G	Influenza	12 hours	50	Intravenous	" Detoxication "	12 hours Apparent benefit.	Nil
*5 R. N T	Influenza, relapsing bronchiolitis	12 hours	25	Intravenous	Incomplete " Detoxication "	14 days No benefit	14th day, rash
†6 A E F	Influenza	24 hours	50	Intravenous	" Detoxication "	4 days ? Benefit.	Nil.
7 C F. D	Influenza, chest signs .	20 hours 26 " 32 " 38 "	50 10 10 10	Intravenous Intramuscular " "	" Detoxication " Nil Nil Nil	2 days Apparent benefit	10th day, rash.
8 J F. H	Influenza, chest signs .. .	20 hours 24 " 40 "	50 10 20	Intravenous Intramuscular "	" Detoxication " Nil Nil	2 days Apparent benefit.	Nil
9 K. C. B.	Influenza; apyrexial	20 hours 24 "	50 10	Intravenous Intramuscular	" Detoxication " Cyanosis of hands.	Nil ?	Nil.

IH_2, a large series of treated cases with strictly alternate control cases was needed. The supply of IH_2 serum was exhausted, but a batch of concentrated antiviral serum was made available through the kindness of Dr. R. A. O'Brien This serum, pooled from two horses (IH_3 and IH_4) had been made by Laidlaw, Smith, Andrewes and Dunkin (1935) by inoculation of the horses with ferret material infected with both human and swine influenza viruses It was concentrated by Dr R. A. O'Brien but the concentrate was not quite so potent against human virus as the original IH_2 Unfortunately, the serum proved extremely toxic to human beings Two patients received 25 c.c. intravenously after preliminary small doses, and in both severe reactions developed. In one case immediate deathly pallor and vomiting were followed by rigor and circulatory collapse half an hour later. In the other there was immediate pallor but no other effect for 20 minutes when shivering occurred, and hallucinations and a confusional state developed, but there was no rise of temperature. Fortunately, both patients were well within a few hours. A small intramuscular injection of serum (5 c.c) in a third patient was followed by considerable local swelling and tenderness. Use of this serum was therefore abandoned Thus the observations which have been made are both disappointing and incomplete. The horse serum which had such a definite effect on the virus infection in mice produced an effect in human beings only in large doses, and this effect was not observed in a sufficient number of cases or with sufficient controls to establish it as specific in nature.

Finally, the effect of human convalescent serum was tried in one patient The serum was made available through the courtesy of Professor Fraser, having been collected by Dr. A. G Scadding and Dr. A A. Miles, of the British Post-graduate Medical School from a case of typical influenza during the epidemic. Thirty-six c.c. of serum intravenously seemed to have a definite paling effect on the patient's flush but the facies was not fully restored to normal The temperature reached normal the day after administration of the serum but subsequently rose to 99·2° F on the 3rd and 4th days. The antibody content of the serum was estimated in the laboratory and found to be about 1/35th of that of the concentrated horse serum IH_2 No conclusions can be drawn from this isolated observation

SECTION III

THE BLOOD PICTURE IN EPIDEMIC INFLUENZA, WITH SPECIAL REFERENCE TO THE LEUCOCYTE COUNT

By D. L. Hughes

A study of the blood picture in epidemic influenza was undertaken to see whether a leucocyte count is of aid in diagnosis, and in particular to determine if the widely quoted leucopenia was a feature of the disease.

1.—Material

The blood samples were obtained from young males in the three Services (the Household Cavalry, Windsor; the R.A.F., Uxbridge; and the R.N., Chatham). The majority were recruits of 16–18 years of age living under similar barrack conditions. Unless otherwise stated all the patients were examples of uncomplicated influenza. The cases were of a characteristic type, the influenza virus having been isolated from representative cases.

2.—Methods

Blood samples were taken from the patients at approximately the same hour each day; if circumstances necessitated a change the succeeding samples were taken at the new time. Blood samples were taken from the unrubbed lobe of the ear, mixed in pipettes in a dilution of 1 in 200 with normal saline containing 0.1 per cent gentian violet. R.B.C. and W.B.C. counts were made of a sample from the same pipette in a Burker counting chamber. At Uxbridge counts were made at 24-hour intervals; later at Chatham when an idea of the prevailing leucocyte picture had been obtained they were made at 48-hour intervals. At first R.B.C. counts and haemoglobin estimations (Haldane's method) were made to see if any abnormality was present in these elements, but as none was found this was discontinued.

Blood films were made on slide preparations, stained with Jenner's stain and a differential count made on 100 cells. While it was realized that a count of 100 cells would not give a very accurate picture of the W.B.C. distribution it was thought that any gross deviation from the normal would be recognized, and if present, a further check could then be made by counting 500 cells.

3.—Results

R.B.C. counts.—The average of the R.B.C. counts on 26 patients was 5,200,000 per c.mm. with a range from 4,400,000 to 6,000,000 per c.mm. Haemoglobin values ranged from 82 to 102 per cent and the colour index from 0.84 to 1.0.

W.B.C. counts. Uncomplicated cases.—W.B.C. counts were performed on 40 uncomplicated cases within three days of the onset,

In 37 of these patients the average W.B.C. count was 7,026 per c.mm with limits from 4,000–14,000. Two of them had a leucocytosis one was a ward orderly with a history of malaria (16,000 per c mm and the other had streptococcal tonsillitis (15,000 per c.mm). C these 40 cases, 8 were tested for the presence of influenza viru Four were virus-positive and of the four virus-negative cases tw were afebrile and one was a case of gastroenteritis. The averag W.B.C. count in the virus-positive patients was 7,812 and in th virus-negative it was 7,968 per c.mm. Representative leucocyt counts during the acute stage of the disease will be found in Table 2 and the results are summarized in Table 21.

Follow-up counts.—Twenty nine patients were followed to th twelfth day from the onset. The average W.B.C. count in thes was 6,746 with limits from 3,000–15,500 per c.mm.

Twenty-six patients were followed into convalescence before thei discharge from hospital. Eight maintained counts within norma limits, the average being 6,678 with limits from 4,000–14,000 pe c.mm., eighteen showed a leucocytosis with an average W.B C. coun of 18,525, with limits from 14,500–? 40,000 per c.mm.

Ten patients were followed after their discharge from hospital All showed a persistent leucocytosis after their discharge. The significance of this condition was investigated and will be discussed below.

Complicated cases—Nine patients with bronchiolitis or with pneumonia were followed during the acute stage of the disease. Eight of these had W B.C. counts within normal limits (3,000–14,000 per c.mm) with an average count of 8,605. The other (with influenzal pneumonia) had an average W.B.C. count of 16,200 with limits from 15,000–16,800 per c mm. Three of these patients were virus-positive and three were virus-negative. The average W.B.C. count in the virus-positive was 10,472 per c.mm. and 10,194 in the virus-negative Representative counts during the acute stage of the disease will be found in Table 20.

In the uncomplicated and complicated groups the differential W.B C counts showed no striking feature. In some cases there was a slight relative neutrophilia within the first two or three days of the onset, which soon disappeared, the distribution returning to normal

4.—Discussion

Carrey and Bryan (1935) in an extensive review of the literature on normal W.B C counts found a range of 3,500–15,600 per c.mm when a reliable technique was used. In their own series of 627 counts on 200 normal subjects, which appear to be the most carefully controlled [illegible] they found a range of from 2,700 to 14,000 [illegible] with those of Price Jones, Va[illegible] d the method described above [illegible] fore puncture. They found that 3·7 per cent. of counts were below 5,745 per

TABLE 20

Leucocyte counts on epidemic influenza patients

Patient	Day of disease	Type of disease	Total W B C Per c mm	Polymorphs Per cent	Polymorphs Total	Eosinophils Per cent	Eosinophils Total	Basophils Per cent	Basophils Total	Lymphocytes Per cent	Lymphocytes Total	Mononuclears Per cent	Mononuclears Total
J R C	3rd	Uncomplicated	5 500	70	3 850					29	1 595	1	55
	5th		6 600	67	4 422					27	1,782	6	398
*C K G	2nd		7 500	80	6 000					13	975	7	525
	3rd		5 500	56	3 080	1	55			43	2,365	1	55
*J O	5th		14 000	57	7 980			1	140	34	4 760	8	1,120
	7th		9 000	41	3 690	2	180			52	4 680	5	450
A I W	2nd		8 000	65	5 200					28	2 240	7	560
	3rd		6 500	53	3 445					47	3 055		
D B	2nd		7 000	83	5 810			1	70	15	1 050	1	70
	4th		8 000	50	4 000					50	3 000		
*R F	1st	Bronchiolitis	5 000	84	4 200			2	100	28	1 400	6	300
	2nd		9 000	66	5 940					28	2 520	6	540
*J J	3rd		6 000	61	3 660					38	2 280	1	60
	3rd		10 500	89	9 345					11	1 155		
C S	4th	Influenzal pneumonia	10 000	85	8 500			1	100	13	1 300	1	100
	5th		14 000	81	10 530	1	130			16	2 080	2	280
	8th		11 000	52	5 720					45	4 950	3	330

* Virus positive

TABLE 21

(a) *Uncomplicated influenza. W B.C. counts 1st–3rd day from the onset*

	Total no of cases	No of cases with counts within normal limits	Average of "normal counts"	Range of "normal counts"	No of cases with leucocytosis	Average of leucocytosis	Range of leucocytosis	Virus tested. +	−
W	6	5	5,700	4,000– 7,500	1	16,000	16,000	1	0
U	15	15	7 546	4,500–13 000	0	—	—	1	2
C	19	18	7,833	4,500–14,000	1	15,000	15,000	2	2
Total	40	38	7,026	4,000–14,000	2	15,500	15,000–16,000	4	4

(b) *Uncomplicated influenza. W B C. counts 3rd–12th day from the onset*

	Total no of cases	No of cases with counts within normal limits	Average of "normal counts"	Range of "normal counts"	No of cases with leucocytosis	Average of leucocytosis	Range of leucocytosis	Virus tested. +	−
W . .	2	2	6,000	5,500– 6,500	0	—	—	1	0
U. . .	10	10	6,770	3,000–11,000	0	—	—	2	0
C . .	17	16	7,470	4,000–14,000	1 (1 count)	15,500	15,500	2	2
Total	39	28	6,746	3,000–14,000	1	15,500	15,500	5	2

(c) *Influenza with bronchiolitis and pneumonia. 1st–7th day from the onset* •

	Total no of cases	No of cases with counts within normal limits	Average of "normal counts"	Range of "normal counts"	No of cases with leucocytosis	Average of leucocytosis	Range of leucocytosis	Virus tested. +	−
U .	5	4	8,100	4,000– 9,400	1 (1 count on 5th day of illness)	16,200	15,000–16,800	2	0
C . .	4	4	9,110	6,000–14,000	0	—	—	1	3
Total .	9	8	8,605	4,000–14,000	1	16,200	15,000–16,800	3	3

W. = Windsor U = Uxbridge C = Chatham

c.mm. It would appear therefore that in any large series of blood examinations a small proportion of patients may be expected to have W.B.C. counts below 5,000. Such low counts cannot be considered as evidence of a leucopenia unless they occur with a greater frequency than normal. This point has not been appreciated by previous workers. For the purposes of the present discussion therefore 3,000 to 14,000 W.B.C. per c.mm. are accepted as normal limits.

In reviewing previous work on the white cell picture in acute influenza it becomes apparent that the majority of the figures fall within Price Jones, Vaughan and Goddard's limits of normal (3,000–14,000). The findings in previous epidemics have been tabulated (Table 22). Many workers do not state what they consider to be limits of a normal white cell count, while others (Stone and Swift, 1919; Strouse and Bloch, 1918) claim to have found a leucopenia [illegible] erefore that the majority of the [illegible] eptions, notably those of Matz,

In forty cases of influenza in the present series studied within three days of the onset of the disease, there was no W.B.C. count that could be considered leucopenic, that is to say no W.B.C. count was under 3,000 per c.mm. In two of the patients who had counts above 14,000 other factors were involved (a history of malaria and streptococcal tonsillitis). The average W.B.C. count in this stage of the disease was 7,026 per c.mm. In thirty-nine patients who were followed in the acute stage up to the twelfth day from the onset the average W.B.C. count was 6,746 per c.mm.

It would appear therefore that in the present epidemic the total W.B.C. count was not affected by uncomplicated virus infection, nor do the figures in the literature suggest that a leucopenia was common in previous epidemics.

A number of previous workers have drawn attention to the occurrence of a leucocytosis in convalescence, which in some cases was associated with pneumonia or other lung lesions, but in others appeared to be unassociated with any significant lesions, as in the patients described above. Thus, Gotch and Whittingham (1918) found a leucocytosis on the third or the fourth day of the disease of from 14,000 to 18,000 per c.mm. Synott and Clarke (1918) record W.B.C. counts between 12,000 and 30,000 per c.mm. after two to three weeks. Dwinell (1918) found W.B.C. counts in what appear to be uncomplicated cases from 15,000 to 30,000 per c.mm., and 14 patients when discharged, he notes, had figures over 15,000 per c.mm. Keeton and Cushman (1918) state that 24.3 per cent of their cases showed a leucocytosis with improvement, but they take as their range of normal from 7,000 to 9,000 per c.mm.

The cause of the persistent leucocytosis.—During convalescence there was a high count in a large proportion of patients in the present series. In some instances this persisted for some weeks. It was found in some patients while in hospital, but was most

TABLE 22

The total white cell count in influenza

Authors and date	No of patients	No of counts	Average W B C. counts per c mm	Range of W B C counts per c mm	Remarks
Bloomfield and Harrop (1919)			4,000 and 5,000	2,000 up to normal figures.	The average figures are for the 1st and 2nd day of the disease.
Bunting (1921)				2,600– 9,000	
"				2,600– 4,000	
Yabe (1920)				3,750– 6,900	
"				Under 3,000	
Brem, Bolling and Casper (1918)		3		3,000 10,000	
"				4,000– 8,000	
Blanton and Irons (1918)		5		?	
"		206			
Martin (1918)		406			
Keegan (1918)		174			
Rackmann and Brock (1919)	5		6,700	8,000–12,000	No counts were under 4,000.
Lyon (1919)	28		9,200	4,200–10,000	
"	10		8,500		
"	10				
"					
Gotch and Whittingham (1918)	19, 17, 4, 3 (bracketed)		5,537	2,675– 5,000; 5,000– 7,500; 7,500–10,000; 10,000–11,900 (bracketed)	
Whittingham and Sims (1918)	6			3 000– 4,500	
Matz (1919)	12	83	5,800	2,200–26 200*	Day of admission
"	32	162	5,200	2 000– 3,000*	Fourth day of disease
"	73			3,000– 4,000	
"	133			4,000– 5,000	
"	163			5,000– 6,000	
"	173			6,000– 7,000	
"	215			7,000–10,000	
Forbes and Snyder (1918)	295			Over 10,000	
Synnott and Clark (1918)	50		7,194		
Greig (1920)	700		5,000		
"					
Rosenow (1920)		23			
Dwinell (1919)		1			
			3,600	3,000–29 912	The lowest count recorded was 1,200 per c mm

marked in those men who had returned to barracks Investigations at present in progress suggest that this convalescent leucocytosis was, at least in some instances, an artefact, due to the fact that the blood samples were taken from the unrubbed ear When the ear was rubbed before puncturing or when the blood was withdrawn from the vein a normal W.B C. count was obtained When a normal count was found in the blood from the unrubbed ear it agreed closely with that found in blood from the rubbed ear and from the vein. The R B.C count was the same in all samples

It is known that in certain organs a high white cell count may be obtained from the capillaries while the R B C count remains unaltered, and it has been suggested that when the blood flow is slow there is a leucocyte skimming in the capillaries resulting in the presence of an abnormally high number of white cells This phenomenon has not been recorded as occurring in skin capillaries It offers, however, a possible explanation of the results obtained and it is being investigated

During the early stages of infection all the patients in the present series were warm in bed and showed a typical flush suggesting that the superficial circulation was brisk It is believed therefore that the blood counts during the acute stage may be accepted (Table 20) They agree with the results obtained elsewhere (Scadding, 1937) during the present epidemic when the ear was rubbed before sampling

As has been indicated above a leucocytosis during convalescence has been reported by many investigators of the 1918 epidemic However, they do not mention the technique employed and so it is not possible to determine how far the same error may have been present. The elucidation of the duration and the character of this leucocytosis in certain patients during convalescence must clearly await further investigation

The accounts in the literature of differential white cell counts are somewhat contradictory Braxton Hicks (1919) generally found a qualitative increase in the mononuclear cells Harry (1921) records a relative lymphocytosis in mild cases, the eosinophils being entirely absent or diminished Synott and Clark (1918) state that there was a relative percentage increase of lymphocytes In some cases of Greig's (1920) there was a relative increase in the polymorphonuclear leucocytes. Martin (1918) found a normal distribution of the W.B C Thonnard Neumann (1928) attached importance to the percentage of young polymorphonuclear leucocytes at the onset of the disease In Blanton and Irons' (1918) patients the neutrophils showed but a slight increase, and there was no conspicuous lymphocytosis. Bloomfield and Harrop (1919) found, in the acute stage of the disease, an absolute decrease of polymorphonuclear leucocytes with a relative lymphocytosis In some patients the lymphocytes were also decreased Gotch and Whittingham (1918) noted a relative neutrophilia with a slight increase in the number of small lymphocytes when the leucocytosis commenced The reverse occurred in a previous epidemic. Matz (1919) found the majority of his patients had a

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Greig (1920)		23		3,000–29 942	The lowest count recorded was 1,200 per c mm
,,		1		2,655	
Rosenow (1920)			3,600	5,000– 9 000	
Dwinell (1919)				7,000– 9,000	

* Pneumo

marked in those men who had returned to barracks Investigations at present in progress suggest that this convalescent leucocytosis was, at least in some instances, an artefact, due to the fact that the blood samples were taken from the unrubbed ear. When the ear was rubbed before puncturing or when the blood was withdrawn from the vein a normal W B C count was obtained When a normal count was found in the blood from the unrubbed ear it agreed closely with that found in blood from the rubbed ear and from the vein. The R B C. count was the same in all samples.

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normal distribution. Forbes and Snyder (1918) record a relative lymphocytosis. In 70 children, Milio (1920) found the polymorphonuclear leucocytes diminished and an increase in the lymphocytes in 75 per cent. of his cases There seems to be general agreement in the above literature that when a leucocytosis occurred the neutrophils were increased.

In this study the differential W.B.C. counts performed on 100 cells have shown no striking change The authors quoted above in most instances do not state how many cells were counted; it is therefore difficult to know how accurate their results are. Bearing in mind the small number of cells counted in this series it may be said that some cases showed a slight neutrophilia in the first two or three days, which did not persist.

5.—Conclusions

(*a*) Thirty-eight uncomplicated cases of influenza seen during the acute stage of the disease had a normal W.B C. count.

(*b*) The blood count records of previous epidemics are reviewed. With few exceptions the figures found confirm the present finding of a normal initial W.B.C. count.

(*c*) A leucocytosis during convalescence has been noted by previous workers Insufficient data have been collected in the present study to confirm this observation.

I would like to acknowledge my indebtedness to Dr. Janet Vaughan for her advice and help.

SECTION IV

RECOVERY OF VIRUS DURING THE 1936–7 EPIDEMIC

By C. H. Andrewes, Wilson Smith and C. H. Stuart-Harris

A.—Earlier Work on Isolation of Influenza Virus

A virus was first isolated from cases of epidemic influenza in 1933 by Smith, Andrewes and Laidlaw by means of the intranasal inoculation of ferrets with bacteriologically sterile filtrates. The virus caused a characteristic disease in these animals, which bore certain resemblances to human influenza. After an incubation period of approximately 48 hours there was a temperature response, usually of diphasic character, accompanied by symptoms such as sneezing, yawning, nasal discharge and obstruction resulting from inflammation of the turbinates and nasal sinuses. Although general symptoms like anorexia and muscular weakness were present, the virus remained localized in tissues of the respiratory tract. The disease could be transmitted either by contact of sick and healthy ferrets or by direct intranasal inoculation of exudates or emulsions of tissues from the respiratory tract of sick animals. All other methods of inoculation were found to be innocuous.

This work was confirmed in the following year by Francis (1934), and since then virus strains have been isolated from cases in many countries and from several epidemics in England and America (Burnet, 1935; Andrewes, Laidlaw and Smith, 1935; Smorodintseff *et al.*, 1936; Brightman and Trask, 1936; Bijl and Dommisse, 1936; de la Rivière and Chevé, 1937, Hoyle and Fairbrother, 1937)

B.—Methods used to Isolate and Identify Viruses

In the 1936–7 epidemic influenza virus was recovered from at least 39 and perhaps 44 cases by the methods employed in previous years

Patients believed to be suffering from influenza were instructed to gargle about 15 c.c. of sterile saline and to spit the garglings out into a sterile container. A few c.c. of Hartley's broth were immediately added. Broth helps to preserve the virus if the ferret cannot be inoculated at once; it is added after gargling because saline is more [illegible]

which had been kept at −2° C. for 2 months before the test was made and from another lot which had travelled by air mail from Berlin. The garglings were always taken as early in the disease as possible, preferably within 48 hours of the onset, but a positive result was obtained as late as the 4th day in one instance of uncomplicated influenza and even on the 6th day from a patient with influenzal pneumonia.

TABLE 23

Recovery of virus from uncomplicated cases

Name	Place	Day of disease	Remarks	If dried for further study	Time of keeping washings (days).	Ferret		
						Take.	Inoc ferret later immune to W.S.	W.S 1 immune ferret immune to new strain.
1 CRI	Windsor	2		+	0	+	Yes	Yes
2 GAT	,,	1		+	1	+		
3 FLA	,,	2	Vaccinated 3 days previously	0	2	+	Yes	
4 MYN	Uxbridge			+	3	+		
5 FOR	,,	1	Bronchiolitis	+	0	+		
6 AIT	,,	2	,,	+	0	+	No	
7 RIC	,,	2		0	0	0		
8 BUR	,,	2		+	0	+		
9 ORD	Chatham	? 2 or 4		0	1	+	Yes	
10 HAF	,,	2	Bronchiolitis	+	1	+		
11 TAL	,,	1	,,	+	2	+		
12 WAL	,,	2	Very mild case	0	2	?0		
13 COW	,,	1		0	2	+		
14 FLE	,,	2	Bronchiolitis	0	5	?0	Yes	
15 ELL	,,	2		+	1	+		
16 RIM	Shorncliffe	3	Vaccinated 1 day previously	0	1	?0	Yes	
17 ADA	,,	1		+	1	+		
18 COO	,,	2	Meningeal symptoms in ferrets caused by pneumococci.	+	2	?0		
19 WAR	,,	3		+	2	+		
20 HEM	,,	3	Bronchiolitis	+	1	+		

Cases 1 to 20 were from the epidemics among the services which have been described in this report. Fifteen of the 20 garglings tested were definitely positive. Case 16 was probably positive also; the inoculated ferret showed poor symptoms and a maximum temperature of 103·8° F. but on being tested later with W.S. virus it was found to be immune.

Nos. 21 to 30 were from civilian cases from the London area; Nos. 36 to 38 were from boys at boarding schools; Nos. 39 and 40 were garglings sent by air mail from the continent; No. 39 from Berlin was positive, while No. 40 from Budapest gave a negative result. We did receive, however, from Dr. R. M. Taylor, of the International Health Division of the Rockefeller Foundation, a Budapest strain of virus after it had been passed through 1 or 2 ferrets, and with this we were able to infect ferrets and mice.

2—"EXPERIMENTAL" MATERIAL

In addition to the simple influenza cases we tested garglings from 22 other cases which we considered, for one reason or another, to be less likely to yield virus (see Table 24). We were, in fact, no longer merely determining from how many typical cases virus could be recovered, but were venturing into less explored regions in the hope of learning more of the habitat of our virus Thus two cases with gastric symptoms were tested; one (No 41) [illegible] developed later, yielded virus;

[illegible] in association with typical [illegible]

Table 24 we record the duration of the relapse and, in brackets, the total duration of the illness at the time of the relapse and of taking the garglings. Fourteen of the samples recorded in Table 24 were [illegible]

[illegible] from several vaccinated persons who later developed fever even though the symptoms were far from typical of influenza. As will be seen, we recovered influenza virus from four people who developed symptoms of influenza 2–5 weeks after their vaccination.

3.—CASES OF PNEUMONIA

From 11 cases diagnosed as influenzal pneumonia we only recovered virus on one occasion (Case 66) or perhaps two (Case 69). (See Table 25) This relatively poor success was surprising. It is true that the cases were tested later in their disease than were the majority of simple influenza cases, from none of the pneumonias were washings taken earlier than the third day, while most of the others were tested on the first or second days Yet virus was recovered from at least five uncomplicated cases as late as the third

TABLE 21

Recovery of virus from atypical cases, etc.

Name	Place	Day of disease	Remarks	If dried for further study	Time of keeping washings (days)	Ferret: Take	Ferret: Innoc. ferret later immune to W.S.
41 GOO	Windsor	2	Acute gastric onset	+	2	+	No
42 WHI	Chatham	2	Gastro-enteritis	0	1	0	
43 NIX	Uxbridge	2	Afebrile case	0	2	0	No
44 MOI		4		0	2	0	No
45 BIC 2	Uxbridge	1 (16)	Relapse case	0	1	0	No
46 GHD 2	Chatham	1 (10)		0	1	0	No
47 HAI 2		1 (9)		0	1	0	No
48 ELC	Shorncliffe	2	Streptococcal tonsillitis	0	1	0	No
49 BRO		2	Coryza	0	1	0	No
50 BUT	Hampstead	3	Vacc. 3 weeks previously	0	0	0	No
51 BLI	Mill Hill	2	1 week Coryza	0	0	0	No*
52 MAR	London	4	10 days Afebrile	0	0	0	
53 CLA	Hampstead	2	18	0	0	0	
54 HAY	Windsor	4	21	+	2	+	No
55 MM	Hampstead	4	23	0	1	0	Yes
56 DAV	Aldershot	3	16 (erythema nodosum)	+	1	+	No
57 PAR	Hampstead		5 weeks	+	0	+	
58 COD	Windsor		7	0		0	
59 STZ	Hampstead			0		0	
60 STI	London	1	6 weeks previously (afebrile)	0	1	0	
WED	Hampstead	4	2½ months (septic pharyngitis)	0	0	0	No
TAG	Colchester		2	0	0	+	No
GAW				0	0	0	

* Immune to TAL strain but not to W.S. strain.

TABLE 25

Recovery of virus from garglings from pneumonia cases

Name	Place	Day of disease	Remarks.	If dried for further study.	Time of keeping washings (days)	Ferret. Take.	Ferret. Inoc. ferret later immune to W S
64 PUR	Hammersmith	10		0	1	0	0
65 MAR	"	4		0	2	0	0
66 STE	Uxbridge	5		+	1	+	+
67 MIL	Chatham	3	T B pneumonia	0	2	0	0
68 FIT	"	3		0	2	0	?
69 SMI	"	4	"Atelectatic pneumonia"	0	7	?0	+
70 TIE	"	5		0	1	0	0
71 WS2	Hampstead	3	Vacc 6 weeks previously pneumonia Pneumococcal lobar	0	0	0	0
72 BAK	Uxbridge	3		0	2	0	0
73 WAT	Shorncliffe	3	Haemolytic strep. pneumonia	0	4	0	0
74 MUR	Hammersmith	3		0	21	0	0

TABLE 26

Recovery of virus from lungs of pneumonia cases post-mortem

Day of disease	Remarks	H dried for further study	Time of keeping washings (days)	Ferret: Take	Ferret: Inoc. ferret later immune to W.S.	Ferret: W.S.-immune ferret immune to new strain
2	St. aureus in cultures	+	1	+	? No	*
8	H. influenzae in cultures	0		0	No	
11	Pneumococci	0	1	0	No	
4	St. aureus	+	1	+		
5				+		
	Dried lung tested. H. influenzae in cultures	0		0		

* Of two W.S.-immune ferrets one proved susceptible, another not

day, so that it is doubtful how far the time of obtaining the sam can explain the results. It is possible that when the virus atta the lungs, there is less of it to be found in the upper respiratory tra

4.—Post-mortem Material from Cases of Influenzal Pneumonia

Pathologists* at three London hospitals kindly provided us wit fresh material from autopsies on 5 influenzal pneumonia patients (see Table 26). Three of these 5 patients died within 5 days of the first onset of symptoms and from lung-suspensions from each of the three we recovered influenza virus It is of interest that in these three instances, the lungs gave a plentiful growth of *Staphylococcus aureus* on cultivation. Material from 2 cases dying some time after the onset of symptoms (11 and 8 days) failed to yield virus, nor was any obtained from some dried human pneumonia lung sent us by Professor Tulloch from Dundee. Since we have failed to recover virus from garglings taken late in the disease, it is not surprising that we failed also to find it in the lungs at a late stage. It would be unwise to draw conclusions from the striking bacteriological findings in only three cases; but these at least suggest the possibility that when *Staphylococcus aureus* is a secondary invader, death is apt to occur more quickly, at a time when virus is still easy to recover.

The results of attempts to recover virus during the 1936–1937 epidemic may be summarized thus:—

TABLE 27

Summary of tests for virus

	Number tested	*Positive*	*Doubtful*	*Negative*	*Per cent positive*
Simple cases	40	30	4	6	75
Atypical and vaccinated cases	23	5	0	18	22
Pneumonias (garglings)	11	1	1	9	9
" (lungs *post mortem*)	6	3	0	3	50

D.—Adaptation of the Virus to other Species

Andrewes, Laidlaw and S... independently that ferret into anaesthetized mice ma in a small percentage of t ...animals. The virus ...ary consolidation pulmonary disease was established by methods of culture, filtration and virus neutralization with specific immune sera Adaptation of the virus results from serial passage through mice so that mouse

* We desire to express our thanks to the pathologists referred to Prof. J McIntosh of the Middlesex Hospital, Prof W D Newcombe of St Mary's Hospital, and Dr J G Scadding of the British Postgraduate Medical School.

strains have been obtained which will infect 100 per cent of inoculated animals and if given in sufficient amount, will kill most of them within a few days. The mouse disease is essentially a virus pneumonia; unlike the ferret disease, it exhibits no symptoms of nasal involvement and no gross pathological changes elsewhere than in the lungs. It is not transmissible by contact but only by direct inoculation of virus into the respiratory tract under anaesthesia.

Other species, subsequently shown to be susceptible to infection with ferret virus, are swine (Elkeles, 1934; Shope and Francis, 1936) and hedgehogs (Stuart-Harris, 1936).

Adaptation of virus strains to mice in 1937.—Strains of influenza virus recovered in England in 1935 were with one exception, readily adapted to mice (Andrewes, Laidlaw and Smith, 1935). In that year 4 strains coming from an epidemic at Shorncliffe and 1 from London produced lung lesions in mice after 2 or 3 passages in ferrets, though attempts to infect mice directly with human garglings or after only 1 ferret passage were unsuccessful. A second strain from London, BH, failed to produce lesions in mice after 3, 5, 7 and 9, but did so after 13, ferret passages. In 1937 we at first found it much more difficult to infect mice with recently isolated strains than we had done in 1935. Hoyle and Fairbrother also report, of their tests with viruses isolated in 1937, even after 5 to 7 passages in the ferret, mice could not be consistently infected. Later however, we found that failure to infect mice was often only apparent; most viruses of human origin would, after only 1 or 2 ferret passages, produce an inapparent infection in mice. If serial passages were made from these, lung lesions would be seen after passing a few times. We accordingly adopted the following scheme for adapting viruses to mice. We started in most instances with dried turbinates and nasal mucosa coming from the first ferret inoculated with human garglings. This was ground up with about 3 c.c. of broth-saline and inoculated into a ferret intranasally. The ferret was killed after 3 or 4 days and an emulsion of its nasal mucosa centrifuged and inoculated to 6 young mice under ether anaesthesia. Three of the mice were killed after 3 days and passage made from their lung-emulsions to more mice. The other 3 of the first lot of mice were killed 6 days after inoculation. After strains had once begun to produce lesions they often took 5 or 6 days to do so and we had reason to believe that by this time we had already passed the optimum time for securing virus for passage. It was therefore thought best to kill some mice after 3 days for passage, and others after 6 days to see whether macroscopic lesions were being caused. If 2 or 3 lots of mice in series had been inoculated and still no lesions had appeared, we infected a ferret intranasally to make sure that virus was still being carried on. Fortified by a positive result, we could continue our passage-by-faith. Ferrets inoculated at this stage were allowed to recover and were bled out from the heart a fortnight later to furnish serum for immunological studies. When, after 3 or more serial transfers, lung lesions in mice were finally obtained,

they became progressively better during the next few passages. A test was made to show that an active filtrate through a collodion membrane could be obtained, and then cross-neutralization tests were carried out as described later. Details of adaptation of viruses to mice are shown in Table 28. It will be seen that one strain (CRI) infected ferrets readily but, in two separate trials, rapidly died out on mouse-passage. Another (KOP) was passed through 2 ferrets and then into mice. It survived in the mice through at least 11 transfers but produced no visible lesions and then it died out. A second attempt to adapt the KOP virus to mice after 7 ferret passages was quickly successful.

TABLE 28

Adaptation of 1937 viruses to mice

Strain	*Numbers of ferret passages before serial passage in mice was begun*	*Numbers of mouse passages after which infectivity of material for ferrets was tested and result of test.*	*Numbers of mouse passages before lung lesions in mice were produced*
TAL	13	1 (+) and 3 (+)	3
BUR	4	3 (+)	7 (? 6)
VIZ	3	No test	1
GAT	2	2 (+)	5
BAU	2	No test	3
MID	2	3	5
KOP (1st attempt)	2	2 (+) and 11 (+) 16 (−) and 17 (−)	Neg after 18
KOP (2nd attempt)	7	No test	3
ADA	3	6 (+)	2
CRI (1st attempt)	2	2 (−)	Neg after 4
CRI (2nd attempt)	3	4 (−)	Neg after 5

E.—Direct Isolation of Virus by Means of Mice and Tissue Culture

Until 1937 all attempts to isolate virus from human material by means other than ferret inoculation met with failure except that in 1936 Smith and Stuart-Harris reported the direct infection of mice with throat washings from a patient accidentally infected in the laboratory with a highly virulent mouse-adapted strain of virus. In 1937 Francis and Magill (1937, b and c) succeeded in transferring virus from human washings directly to both mice and tissue cultures —in each case, however, a number of passages were necessary before the virus was able to produce signs of infection in mice.

We only made a few attempts, all of them unsuccessful, to infect mice directly from human material; during the epidemic the available mice were needed for other aspects of the work. It is highly probable that we should have succeeded in direct man to mouse transfer if we had known then what came to light later, that a virus can produce an inapparent infection in mice and only after several passages give visible evidence of its presence.

F.—The Immunological Relationships of Virus Strains

For a long time it was believed by all workers that the strains of human virus isolated in different epidemics and in different countries were immunologically identical. It is undoubtedly true that most of them are extremely closely related, but Magill and Francis (1936, b) obtained evidence that two strains which they had previously regarded as identical were in fact somewhat different. Our experiences in the 1936-37 epidemic confirm Magill and Francis's finding that all strains are not identical. The results of the cross-immunity experiments in ferrets already described showed that in most instances ferrets immune to the W.S. virus were also immune to our new strains and conversely. Such a result is not, however, to be taken as proof that the viruses are identical, for the W.S. and swine influenza viruses may immunise one against the other in ferrets, though serological differences between these two viruses are easy to demonstrate. Cross-neutralization tests in mice afford a much more reliable guide to antigenic relationship.

I.—Cross-Neutralization Tests

The reagents used in cross-neutralization tests were :—

(1) *Virus.* To obtain the best yield of virus at least 6 mice were killed usually 2 or 3 days after infection with a virus filtrate. Five per cent suspensions of their lungs were made in a 1 : 1 broth – saline mixture; these suspensions were centrifuged at low speed, clarified through a bed of asbestos pulp and then filtered through a gradocol collodion membrane of average pore diameter 0.6 to 0.8μ (cf. Andrewes and Smith, 1937).

(2) *Ferret sera.* Ferrets were bled out from the heart under chloroform usually 14 days after intranasal infection. 1 : 5000 merthiolate was added to these and other sera as a preservative.

The sera were inactivated at 56° C. for 30 minutes before use. Fresh unheated ferret and other sera are toxic for mice and may themselves give rise to lung lesions.

(3) *Rabbit sera.* Magill and Francis (1936) employed immune rabbit sera in the experiments in which they were able to distinguish between two influenza strains of human origin. Their rabbits were given a single dose of living virus intraperitoneally and bled 9 to 15 days later. Sera obtained later than this or after repeated inoculations were less specific. We prepared a few sera in rabbits by the same technique.

(4) *Horse sera.* The preparation of the immune horse sera H12 and H14 by hyperimmunization with ferret material has been described previously (Laidlaw, Smith, Andrewes and Dunkin, 1935).

Mixtures of equal quantities of virus and various dilutions of serum were left in contact for an hour at room temperature and then tested intranasally on groups of 4 mice; 0.05 c.c. amounts were dropped into the noses of the mice under ether anaesthesia. Mice were killed after 4 or 5 days and their lungs examined for lesions. The reciprocal of the highest final serum dilution which would prevent the development of any lung lesions was taken as the serum titre.

In comparing the activity of many sera against a number of viruses it was clearly necessary to take into account the probability that filtrates of different strains contained different amounts of

virus. Moreover, the results of [illegible]
and on [illegible]
in [illegible] a reliable guide to the
am[illegible] contained in it. Neutralization tests could be interpreted as indicating either the identity or non-identity of two virus strains only if complete cross-neutralization tests, using each virus and antisera against each virus gave clean-cut results. Table 29 shows the results of such an experiment, involving 3 viruses. The W.S. virus, which had been propagated in mice for over 2 years, was much more virulent for mice than the other strains and was therefore diluted when being compared against them.

TABLE 29

Cross-neutralization tests with 3 strains of virus

Sera	*Viruses.*		
	W S 1 1,000.	*TAL*	*GAT.*
Anti-W S	**250**	10	10
Anti-Tal	10	**1,250**	50
Anti-Gat	50	10	**1,250**

The serological comparison of different influenza strains has only just begun and it is hoped to include a large number in the study. Only the preliminary results with a few will be described now. The strains so far studied are:

W S isolated in England in 1933
Phil isolated in U S A in 1934. (Francis.)
PR8 isolated in West Indies in 1934. (Francis.)
B H isolated in England in 1935
SIL isolated in Russia in 1936 (Smorodintseff *et al*)
KOP isolated in Germany in 1936
TAL, BUR, GAT, BAU isolated in England in 1937.
VIZ isolated in Hungary in 1937 (Taylor.)

The hyperimmune horse serum was of no value in distinguishing between strains, having too broad a range of neutralizing activity. This finding was to be expected in view of Magill and Francis's results with rabbit sera On the other hand, convalescent ferret sera showed clean-cut differences between certain strains Cross-neutralization was seen only in low serum dilutions, while neutralization against homologous virus occurred up to a high titre Table 29 speaks for itself and indicates that the W S , TAL and GAT strains are undoubtedly distinct

The cross-tests undertaken up to the present between the available strains have placed them in 3 groups The W S , B H. and SIL strains fell into one , the Phil, PR8, KOP, TAL, BAU and VIZ into

another, while GAT remains at present the sole representative of the third group. Strain BUR has affinities with all 3 groups.

Strains of one group did not necessarily react precisely alike with all sera. While sera prepared against one member of the TAL group would neutralize any other of that group to a high titre, usually 1:250 or better, yet there was noted a tendency for a slightly higher titre against the strictly homologous strain. Further an anti-W.S. serum neutralized members of the TAL group to a varying extent. It seemed possible that the three groups had each their own major antigen and that individual strains in a group might have greater or smaller amounts of antigens in common with those of some other group.

It has already been mentioned that swine influenza virus has serological relationships with human strains; the relation is, however, more distant than that existing between different groups of human viruses. No swine influenza antisera had any effect on the human strains under study nor had convalescent, as distinct from hyperimmune, anti-human-influenza sera upon the porcine virus.

Sera were prepared against W.S., SH, B.R., Phil, PRS, TAL and swine influenza viruses in rabbits by Magill and Francis's technique. The results were in general the same as with the ferret sera described above, though the titres were much lower. Rabbit sera were not more specific than ferret sera, though they, like the ferret sera, were much more specific than hyperimmune horse sera.

We considered the possibility that the W.S. virus might have altered in its antigenic make-up in the course of 150 passages through mice. Comparison of the mouse-adapted strain with one which had been passed 210 times through ferrets but never through mice revealed no differences. We made tests against each strain using sera prepared against each strain in ferrets and in rabbits.

2.—Antibody-Absorption Tests

One might reasonably hope to classify influenza viruses with greater precision by means of absorbed sera. It proved in fact possible to absorb out antibody from an anti-W.S. serum with suspensions of homologous virus but it was necessary first to dilute the serum almost to the limits of its efficacy. Such a dilute serum was mixed with a centrifuged 5 per cent suspension of infected mouse lungs, and absorbed for 2 hours at 37° C. and overnight in the cold. The excess of living virus was then disposed of either by heating to 56° C. for 30 minutes or by filtration through a graded collodion membrane (average pore diameter 0.6 µ) which would retain virus while permitting antibodies to pass. It was possible in this way to demonstrate absorption of W.S. antibody by living W.S. virus suspensions, by virus filtrates and by formolized virus suspensions, while suspensions of normal mouse lungs and of swine influenza virus failed to absorb. Unfortunately these experiments have only proved successful as yet within such a narrow range of serum dilution that they have not contributed anything of great value to the attempt at antigenic

of typical cases of the epidemic influenza prevalent between December, 1936 and March, 1937. The findings of ourselves and others in previous epidemics are thus abundantly confirmed. The viruses recovered in 1937 cannot be certainly distinguished from those obtained in other years by means of cross-immunity tests in ferrets nor by the aid of hyperimmune horse serum. Immunological study by means of sera of recently convalescent ferrets or of certain rabbit sera does however separate the viruses into different serological groups. Those prevalent in 1937 seem, so far as our studies have gone, to be different from those recovered in England in previous years. The differences encountered are probably of sufficient magnitude to play an important part in attempts at prophylaxis; they are also likely to be of first-rate importance in future epidemiological studies.

analysis of different strains. Successful antibody-absorption experiments with influenza virus have previously been reported by Smorodintseff *et al.* (1936)

3.—Cross-Immunity Experiments

We have carried out a few active immunity experiments in mice, crossing one strain against another and employing the technique described elsewhere (Andrewes and Smith, 1937).

Protocols of one experiment are given in Table 30. The mice in this experiment were immunized by injecting 0·2 c.c. of living unfiltered mouse lung virus subcutaneously and a fortnight later 0·25 c c of similar material intraperitoneally. For the immunity test after a further fortnight, virus filtrate was given intranasally. As the TAL virus was not sufficiently virulent to kill, all the mice in the experiment were sacrificed after 7 days and examined for lung lesions

TABLE 30

Cross-immunity test between W.S. and TAL viruses

Immunized with: Virus	Immunized with: Titre of virus in immunizing doses	Tested with: Virus	Tested with: Titre of virus used in immunity test.	Results of immunity test: Died	Lung lesions ++	Lung lesions +	Normal	Total No in group
Nil		W S 1 1,000	10^3	5	2	0	1	8
W S.	10^6 and 10^7	W S. 1 1,000	10^3	0	0	0	9	9
W S.	10^4 and 10^5	W S 1 1,000	10^3	0	1	1	10	12
1 100 TAL	10^3 and 10^4	W S 1 · 1,000	10^3	0	3	3	6	12
Nil	—	TAL	10^3	0	6	2	1	9
W S	10^6 and 10^7	TAL	10^3	0	2	4	4	10
W S	10^4 and 10^5	TAL	10^3	0	1	4	7	12
1 100 TAL	10^3 and 10^4	TAL	10^3	0	0	1	9	10

This experiment indicates that the W.S strain may immunize mice well against the homologous virus but less effectively against one of another group such as TAL. Conversely, the TAL virus immunizes well against TAL but poorly against W.S virus. Such results suggest that the antigenic differences encountered are likely to have practical importance in prophylaxis in man and not merely academic interest

G.—Summary of Section IV

The foregoing section describes the laboratory investigations carried out in conjunction with the clinical studies recorded in Section II Influenza virus pathogenic for ferrets—and, after adaptation, for mice also—has been recovered from a high proportion

of typical cases of the epidemic influenza prevalent between December, 1936 and March, 1937 The findings of ourselves and others in previous epidemics are thus abundantly confirmed The viruses recovered in 1937 cannot be certainly distinguished from those obtained in other years by means of cross-immunity tests in ferrets nor by the aid of hyperimmune horse serum Immunological study by means of sera of recently convalescent ferrets or of certain rabbit sera does however separate the viruses into different serological groups Those prevalent in 1937 seem, so far as our studies have gone, to be different from those recovered in England in previous years The differences encountered are probably of sufficient magnitude to play an important part in attempts at prophylaxis, they are also likely to be of first-rate importance in future epidemiological studies

SECTION V

STUDIES ON ANTIBODIES IN HUMAN SERA

By C. H. ANDREWES, WILSON SMITH AND C. H. STUART-HARR

We have carried out a number of observations on the neutralizi activity for influenza virus of human sera. These include tes made on sera from normal persons at different periods in an epidem cycle, from influenza convalescents and from contacts. Most of tl observations were made before 1937 at a time when the existence c several serological strains of human virus was not known. Since a the tests were made against one strain of virus (W.S.), caution necessary in judging their significance. In future, similar studies wi have to embrace a number of strains. It will, however, be clea from what follows that tests against the W S virus have yielde much information of interest.

A.—Variations in the Antibody-level of the Population in and near London

The distribution of antibodies in the normal population has bee

epidemic of that year, we found antibodies present in almost al the samples examined. At that time we tested sera for the presence of antibodies by mixing them with diluted virus obtained from ferret tissues and inoculating the mixture intranasally into a ferret; failure of the ferret to contract influenza was taken as evidence that the virus had been neutralized This was a crude method, and it was not possible, for reasons of expense, to titrate the sera We have, therefore, no accurate information as to the antibody-level of the community in 1933 In 1934, when the mouse had been found to be susceptible to influenza, it became possible to estimate the amount of antibody in human sera by the technique which has been described on p 107 of this report.

Between October, 1934, and October, 1935, we estimated the antibodies in a number of human sera, particularly in relation to their level in different age-groups (cf. Andrewes, Laidlaw and Smith, 1935) Many of them were sent to us from the United States, many were from people recently convalescent from influenza and only twenty-three of them, coming from Londoners over 10 years of age who had not recently suffered from influenza, may be taken as strictly comparable with the sera we have examined subsequently. In all neutralization tests set up we included a standard serum, one

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t of

this standard serum. All the human sera were assessed in terms of this horse serum, as equal to the standard (= S), one-fifth as strong as the standard (= S/5) and so on. Sera weaker than S/125 could be regarded as having no demonstrable antibody under the conditions of our tests. Our 1934–35 sera had in the main fairly good antibodies; 4 out of 23 of the samples were as potent as the standard, while 17 or 74 per cent had a potency of S/25 or better (see Chart 17).

In the summer of 1936 we observed that in a number of samples of serum examined the antibodies were very poor compared with the values encountered a year earlier. We accordingly thought it worth while to examine larger numbers, first in order to determine whether the level of antibodies in the community had really fallen, and, secondly, to acquire data on a large enough scale to enable us to establish a base-line with which the findings of subsequent years could be compared. Sera examined between June and October, 1936, came from 4 groups of persons.

(1) *A small group* of 12 adult Londoners, mostly workers at the National Institute for Medical Research at Hampstead.

(2) *Thirty men of the Royal Air Force* stationed at Eastchurch, Kent. These were aged 16 to 25 years and had only recently joined the Air Force, many of them coming from country districts. We should not have been surprised to find their antibodies lower than those from an urban population, but, as will be seen, no such difference was found. Sixteen of the men in this group had recently been suffering from a respiratory infection other than influenza; this is discussed on p. 21 of this report. Their sera had the same range of activity as those of 14 normal men of the same unit and they have not, therefore, been treated separately in compiling Chart 17.

(3) *Fifty first-year students at St. Bartholomew's Hospital.*—These men volunteered to allow us to bleed them annually in order that we might try to follow variations from year to year in the antibodies of a population which was likely to remain accessible to us over a period of years.

(4) *Thirty men of the Royal Artillery, stationed at Woolwich.*—These were men forming part of a vaccination experiment to be described later. The sera relevant to the present discussion were those taken as control samples before vaccination.

Chart 17 shows the percentage of persons in each group having a given antibody-level; the distribution of antibodies can be followed from the forms of the curves. It will be seen that the groups whose sera were examined in 1936 have very similar curves, though there is a suggestion of a slightly higher level in the medical students. All the 1936 groups, however, have definitely less antibody than was present in the 1934–5 sera.

The possibility that the antibody titres in the community had fallen in the course of 1 or 2 years raised questions of great importance. A knowledge of such variations might perhaps give us insight into one of the factors controlling the periodicity of influenza epidemics.

Our results must, however, be taken as only suggestive for several reasons. (i) The curve for the 1934–5 sera is based on a small group of only 23 sera. (ii) Very few specimens were taken from the same individual in different years One man, however, bled in February, 1933, soon after an attack of influenza, had a serum equal in titre to the standard ; in December, 1934, the value had fallen to S/5 ; in May, 1936, it was S/25 and in October, 1936, poorer than S/25 The antibody in another individual fell from S to S/125 between March, 1935, and June, 1936. It seems reasonable to expect a fall of antibody in a community, when such has so definitely taken place in individuals. (iii) The mouse neutralization test is not one of very great accuracy. It is possible that the complement-fixation reaction described by

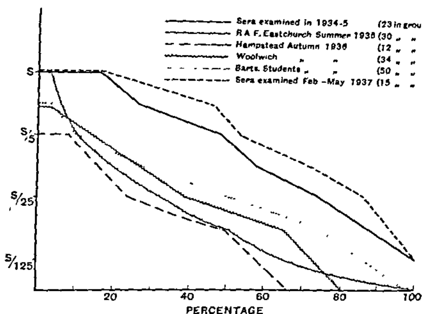


Chart 17

Percentages of persons in different groups having various levels of anti-W S neutralising antibody

Smith (1936) and by Fairbrother and Hoyle (1937) will prove more reliable, but it seems from the results obtained so far that the two tests are measuring somewhat different properties of a serum and further comparative work is necessary before the relative importance of these two properties can be judged (iv) The possibility had to be considered that the fall in antibodies was only apparent, the real change having taken place in the virus against which the antibodies were being tested. We rejected this idea for two reasons First, two sera dried by the lyophile method of Flosdorf and Mudd (1935) had been reconstituted and examined in April, 1935 Other dried samples of the same sera were similarly redissolved and tested in September, 1936, and gave titres practically the same as before.

There was thus no evidence suggesting a change in the virus during the period in question. Further, two sera, one taken in 1935 and one in 1936, were tested against the passage W.S. strain and also

Other evidence that the mouse-passage virus had undergone no antigenic changes is presented on p. 109

B.—Antibodies in the Acute and Convalescent Stages of Influenza

Francis and Magill (1935) found that sera from three patients taken in the acute stage of the disease contained no demonstrable antibodies for influenza virus (PR8 and Philadelphia strains) while good neutralizing properties were present in sera from the same

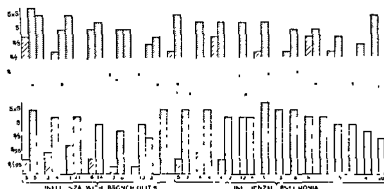


Chart 18

Antibody-levels in sera taken from patients in the early ▨ and later ◻ stages of influenza Numbers beneath the vertical columns indicate on what day of the disease the blood-sample was obtained

uncomplicated disease

Our findings in the 1936–37 influenza epidemic around London are summarized in Chart 18 The sera were obtained from patients at Uxbridge, Chatham and Shorncliffe, the features of the epid

o

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and showed a low antibody-content (average level between S/125 and S/25) Three only of them, taken on the first or second days,

showed a titre of S/5; these all came from patients with uncomplicated influenza We did not actually test the washings from any of these three patients for virus but one at least showed a substantial rise of antibodies during convalescence and was therefore almost certainly suffering from influenza. The diagnosis of influenza in the other two is rather more doubtful. The 23 patients were bled again during convalescence, 6 of them more than once. All showed a rise in antibodies, demonstrable as early as the 8th day of the disease. The rise in 20 out of 23 was twenty-five fold; the three showing a smaller rise were all from men who had a relatively higher antibody-titre to start with. The average convalescent value of these 23 sera and of a further 12 sera taken during convalescence was equal to the standard horse serum (= S), an increase of over twenty-five fold from the value in the acute stage. Cases of uncomplicated influenza, influenza with bronchiolitis and influenzal pneumonia are recorded separately in the chart, but although the complicated cases all showed a very substantial rise, it is not possible to say from the small numbers tested that the final level reached was higher than that in the straightforward cases. There appears in fact to be less contrast between the values for sera from complicated and uncomplicated cases than is recorded by Smorodintseff *et al.* (1936). These authors found in 14 out of 18 sera from influenzal pneumonias a high antibody level which was only attained by 3 out of 14 simple cases

It seemed from the tests on patients who were bled three times [illegible] 12th [illegible] of 5 [illegible] owed some antibody-rise between the 2nd and 5th day of his illness and a definite increase again by the 15th day. In another we found that the high level attained on the 13th day had definitely dropped by the 52nd day, though not nearly to its original level. In a few experiments we tested the power of early and convalescent sera to neutralize a strain of virus (TAL) isolated in 1937 The increase in antibodies during the illness was, in the 5 cases examined, rather greater against the TAL than against the W S virus Two of the [illegible]

upper respiratory disease from which no influenza virus [illegible] recovered showed no rise in neutralizing antibodies in the course of their disease A recent paper by Francis (1937) records similar results in an epidemic occurring in California in the winter of 1935–1936; from this epidemic also no influenza virus was obtained.

C.—Antibodies in Influenza Contacts

The fact that antibodies in the population were apparently higher in 1933–5 than in 1936, even though only a minority of people had suffered from influenza in 1933, led us to suspect that a rise in

pre-epidemic sera it seems more likely that a rise had been produced by subclinical infection than that they represented selected persons who had escaped influenza because of their good antibodies

We only made a few observations bearing on this question during the 1937 epidemic

(i) Sera were obtained on 15th March, 1937, from 6 of the medical students at St Bartholomew's Hospital whose sera had been examined in the previous October None of these 6 men had suffered

in contact with an influenza patient in the same house and he alone showed an increase in his antibodies—from S/125 to a level between S/25 and S/5

(ii) An epidemic of influenza occurred in January, 1937, amongst a unit of Royal Dragoons at Shorncliffe After it had subsided, blood was obtained on 1st February, 1937, from 6 men who had escaped infection though in close contact with men who went sick All 6 showed a high antibody content in their sera, 2 had sera more potent than the standard, while the other 4 showed a value between S/5 and S Though we unfortunately have no information

epidemic

(iii) On 13th January, 1937, about a fortnight from the onset of the influenza outbreak at Chatham, blood was taken from 6 of the sick-berth attendants there who escaped influenza though working in influenza wards One had good antibodies (S/5–S), the others poor to moderately good (< S/25 to S/5) Of the 4 samples which we were able to obtain and test later on (16th March, 1937) none showed a significant rise This result contrasts with the findings in the Royal Dragoons at Shorncliffe, but it is possible that a rise in antibodies would have been detected if we had obtained our first sample before the onset of the epidemic instead of a fortnight after it had begun

(iv) Three of the R A F men from Eastchurch whose sera had been examined in July, 1936, were again bled in May, 1937. None of the three had suffered from influenza meanwhile, yet all three showed a rise in antibodies against W.S virus; the increase was not outside the limits of experimental error in two, but in the third the

rise was more than twenty-five fold, from S/125 to a level higher than S/5.

Further evidence for the acquirement of antibodies by a process of subclinical immunization is contained in the subsection on the [illegible]

D.—Relation between Antibody-Level and Susceptibility to Influenza

Elsewhere in this report (p. 126), we discuss the problem of how far [illegible] imm[illegible] ver[illegible] laboratory infection from a ferret (Smith and Stuart-Harris, 1936), a sample of his serum taken before his infection was available and showed that at the time of infection he had no demonstrable antibodies in his blood. Hoyle and Fairbrother (1937) estimated the complement-fixing antibodies for influenza virus amongst a group of 44 persons at the beginning of the 1937 epidemic. Five cases of [illegible] sons [illegible] nti- [illegible] nza virus was recovered from the 5 cases or whether the diagnosis was purely clinical

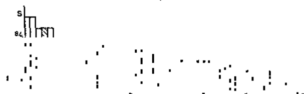
The 50 medical students whose sera we examined in October, 1936, were asked to inform us at once if they developed symptoms suggesting influenza. Three of them got into touch with us at the onset of an infection during January and February, 1937, and from garglings of each of the 3 we recovered influenza virus. Of the group of 50 students, exactly half had poor antibodies against W.S. virus (equal to less than S/25), and all the 3 men fell into this poor antibody group (see Chart 19). When the epidemic was over we questioned 40 of the group who were available and found that besides the 3 men referred to, 5 others had suffered from what, from their description of the symptoms, was very probably influenza. It will be seen from Chart 19 that, from the point of view of their influenzal antibodies, they were scattered at random over the group. One, indeed, had quite a potent serum (= S/5) The results are evidently inconclusive. If one accepts as having had influenza only those men who were seen by us and from whom virus was recovered, there is a suggestion of correlation between poor neutralizing antibodies and liability to infection , but if one accepts the whole eight as influenza cases, clearly there is no correlation at all.

It has been mentioned in discussing the antibodies at different stages of an attack of influenza that three patients, probably suffering from influenza, had antibodies equal to S/5 within a day or two after the onset If this was the value at the time of infection, which is by no means certain, then it is clear that a serum-titre of S/5, which was a relatively high level in the autumn of 1936, did not avail to

protect against infection Once more, however, we emphasize that we have been studying the level of antibodies against the W.S strain of virus, not against the strains most prevalent in the 1937 epidemic.

Chart 19

Antibody levels in 50 first-year students at St Bartholomew's Hospital, October, 1936



A column shaded ▢ thus indicates that the subject suffered from influenza in the 1936–7 epidemic and that virus was recovered from him

A column shaded ▢ thus indicates that the subject gave a history of suffering from influenza in the 1936–7 epidemic but was not seen by us nor tested for the presence of virus

E.—Antibodies against Swine Influenza Virus

Shope (1931) found that the epizootic disease of swine now known as swine influenza is due to the combined action of a filterable virus and an organism (*Haemophilus influenzae suis*) The virus is also pathogenic for the ferret, causing a disease indistinguishable from that produced by human influenza virus (Smith, Andrewes and Laidlaw, 1933) The swine and human viruses are antigenically related, infection with either leaving behind a certain degree of immunity to the other The antigenic relationship can also be

swine influenza was unknown amongst pigs until the time of the pandemic (August, 1918) and on the occurrence of antibodies to swine influenza virus in many human sera Here the distribution of antibodies to human and swine strains is almost identical in the age groups over 10 years but quite different in younger age groups. Antibodies to swine influenza were entirely absent from sera of English children and present in only a relatively small percentage of American children (Shope, 1936 b) The absence or rarity of such antibodies in children under 10 could be explained on the basis that the virus giving rise to them has not been widely spread amongst the human community during the last ten years. In the case of antibodies against the W.S. virus there is no such striking contrast between the levels in children and adults

The neutralizing power of human sera for the swine influenza virus can, however, be explained on quite another basis. There is undeniably some antigenic relationship between the human and porcine viruses. Antibodies to the heterologous virus develop particularly in animals receiving repeated inoculations. Francis and Magill (1936) have suggested that older people who have repeatedly come into contact with human influenza viruses are likely to develop a broader zone of serological activity which may include the swine virus. This explanation is rendered more probable by the results of tests of sera from St. Helena, reported on p. 121. A puzzling fact is that many human sera neutralize swine influenza virus much better than they do the W.S. strain. More knowledge of the antigenic differences amongst human influenza viruses is clearly needed before such findings can be understood.

Chart 20

Percentage of persons tested at two different periods having various levels of swine-influenza neutralising antibody.

In July, 1936, at the time when we found that titres against the W.S virus in human sera were lower than they had been, parallel estimations were made of the antibody present in the sera against swine influenza Sera were examined from 17 Londoners and 23 R A F men from Eastchurch In Chart 20 the results are compared with those obtained in 1934–5 from 23 persons not recently convalescent from influenza. It will be seen that in contrast to the results obtained with the W S virus (Chart 17), there is no evidence of falling off in antibodies to swine influenza in these human sera.

In an attempt to confirm Francis and Magill's suggestion as to the origin of anti-swine influenza antibodies in human sera, we took [illegible] months previously and examined [illegible] .S.) and swine viruses. We [illegible] virus but few or none to the [illegible] reinfected with W S. virus

and their sera again examined; definite antibodies against both strains were now present (see Table 31) The ferrets were left for

failed to support, though it did not negative, Francis and Magill's explanation of the presence of anti-swine influenza antibodies in human sera

TABLE 31

		Antibodies against			
	Virus	*W.S*		*Swine influenza*	
	Number of ferret	*HF1*	*HF8*	*HF1*	*HF8*
Serum taken	Six months after primary infection	S/5–S	S/5	<S/5	<S/5
	Eleven days after second infection	S	25 × S	S/5–S	5 × S
	Six months after second infection	S	S–5 × S	S/25	<S/25

F.—Antibodies in Sera from St. Helena

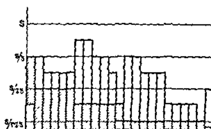
It has been mentioned above that sera were examined from individuals resident on the island of St Helena This was done in an attempt to obtain further evidence with regard to the nature of the virus concerned in the influenza pandemic of 1918. It is known definitely (Ministry of Health Report on Influenza, 1920, Annual Medical Reports of the Island of St Helena) that this island escaped the pandemic and had no outbreak of influenza during the years 1917 to 1921 Islanders who had never left the island and who were alive in 1918 were selected by Dr P B Wilkinson (Medical Officer, St Helena), and sera from 23 of these were collected and sent to Hampstead in October, 1935 The sera were tested against both human (W S) and swine influenza viruses and the results are shown in Chart 21 Only one serum had fair antibody to the W.S. virus, and one also had fair antibody to the swine virus. The remaining sera had negligible W S antibodies, five had small amounts of swine antibody and the rest negligible amounts of swine antibody. The results appeared to confirm the hypothesis which had led to the testing of the sera, namely that the presence of antibodies to the swine virus in European sera was related to the 1918 pandemic of

be related to the fact that at the time the sera were collected, St. Helena had not experienced an epidemic of influenza for at least six years

In June, 1936, an epidemic of influenza occurred on St. Helena and Dr. Wilkinson's account of this is as follows :—

"*During June and July, 1936*, a sharp outbreak of influenza occurred on

disease



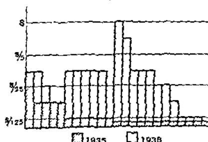


Chart 21.
Antibodies in St. Helena Sera

illness preceded occasionally by a The incubation period appeared to useholds in which one member con- itional symptoms were severe and rigors at onset were noted. Fever in the cases observed in hospital a usually ranged occasionally noted The main symptoms were headache,

sense of prostration reached its off as the fever abated Defervescence appeared to be by *lysis* rather than by crisis in the majority of cases

This picture was typical of the majority of cases and differed from the "common cold" in the abruptness of onset, the higher degree of fever, the slighter involvement of the upper respiratory passages and the profound prostration

respiratory cases was served and both died infections were the

It was impossible to test garglings of patients for virus, but sera from a number of convalescents three months after the epidemic were obtained and some of these showed good antibodies against both W S and swine virus (Chart 22), although there was much

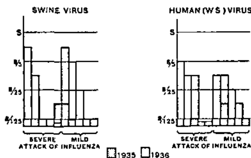


Chart 22

Antibodies in Sera from St Helena Convalescents

variation in the actual antibody content in the different sera, which was perhaps due to the delay between the time of infection and the collection of the sera In December 1936, six months after the epidemic, 22 of the original 23 islanders who were tested in 1935 were again bled by Dr Wilkinson and the sera were examined for antibodies The unshaded rectangles in Chart 21 show the new levels of antibody content and it is seen that a rise above the 1935 level has occurred in many instances Not only have W S antibodies appeared

acquirement of W S antibodies in convalescence might have been expected The unexpected feature of the findings is that antibodies to the swine strain were also acquired by persons who previously had none There is no longer need to relate the 1935 results on the sera to the fact that St Helena escaped the 1918 pandemic, for they could be explained by the absence of influenza on the island for several years prior to 1936 One further point appears in connection with the 1936 results. Three only of the 22 individuals examined had febrile

attacks of influenza during the 1936 epidemic and a further six had colds or vague symptoms. Yet good rises of antibodies occurred in many of the other individuals who had no clinical signs of infection during the epidemic, which strongly supports the conception that sub-clinical infection by the virus is widespread during an epidemic.

G.—Summary

In Section V are described the results of tests on human sera for the presence of neutralizing antibodies against the W.S. strain of virus. These tests were in the main carried out before the existence [illegible] t [illegible] uffer [illegible] V.S.; [illegible] ienza [illegible] ween the level of neutralizing antibodies for W.S. virus in human sera and susceptibility to infection.

The significance of antibodies to swine influenza in human sera is discussed. The results of examining sera from inhabitants of the island of St. Helena suggest that such antibodies may appear as the result of infection with the human strain of virus.

SECTION VI

STUDIES ON IMMUNIZATION OF FERRETS AND MICE

By WILSON SMITH, C H. ANDREWES AND C H STUART-HARRIS

Much of our knowledge concerning the immunological responses to infection or vaccination with influenza virus has been gained by experiments with ferrets and mice In this section we wish to report further experiments which have yielded information applicable to the problem of immunization of man

A.—Immunization of Ferrets against Contact Infection

The normal ferret cannot be completely immunized by prophylactic vaccination against a large dose of virus administered intranasally. Such vaccination, even when repeated doses are employed, confers only a partial immunity The vaccinated animal, if given a test dose of virus, shows definite symptoms and signs of influenzal infection, but the illness is usually of a mild character and of short duration, whilst the temperature response is often curtailed or may even be entirely absent The most important effect of the prophylactic treatment however is revealed when the lung-adapted strain of virus, which causes extensive pneumonia in normal ferrets, is used for the test inoculation—in this case the virus is unable to attack the lungs, which usually remain completely normal or at most show a few small localized foci of consolidation (Smith, Andrewes and Laidlaw, 1935) Moreover, although the upper respiratory tract shows the usual pathological inflammatory changes, recovery of virus from the tissues involved is difficult. Evidently the immunized ferret is in a position to destroy and eliminate virus more easily than the normal ferret It appeared to us desirable to find out whether vaccination of ferrets would protect them against the milder test of contact infection, for it is against this natural mode of infection that it is necessary to protect the human population

The details and results of four experiments are given in Table 32. The plan of each experiment was to run a group of previously vaccinated ferrets and an equal number of untreated controls together with one or two infected ferrets in a small cubicle Not more than one male was included in a group in order to avoid injuries from fighting Care was taken to choose infected animals exhibiting during the period of contact characteristic symptoms of sneezing and nasal discharge At the end of a specified time the animals were removed from the infectious room and each was isolated in a separate cubicle until it was decided whether or no the disease had been contracted Preliminary trials had indicated that 4 hours of such contact were sufficient to ensure infection of normal ferrets , indeed, 3 ferrets so treated showed not only the temperature response and symptoms characteristic of ferret influenza but also

typical influenzal lung lesions. This period was therefore chosen for the earlier experiments. In Experiment 2, however, two of the five control ferrets failed to contract influenza so that for the later tests the period of contact was increased to 24 hours

It is clear that double vaccination with living virus fully protects the ferret against contact infection, for of 10 animals so treated, not one contracted influenza when tested, whereas no fewer than 8 of the 10 controls did so. Vaccination with formolized ferret vaccine, [illegible] 1937).

TABLE 32

Immunization of ferrets against contact infection

Expt.	*Previous immunization*	*Time of contact*	*Result of contact immunity test.*
1	Two subcutaneous doses of living ferret lung virus at weekly intervals	4 hours	0 0
	Untreated controls	*4 hours*	+ +
2	Two subcutaneous doses of living ferret lung virus at weekly intervals	4 hours	0 0 0 0 0
	Untreated controls	*4 hours*	+ + + 0 0
3	Two subcutaneous doses of living ferret lung virus at weekly intervals	24 hours	0 0 0
	Untreated controls	24 hours	+ + +
4	Two subcutaneous doses of formolized ferret lung vaccine at weekly intervals	24 hours	0 + +
	Untreated controls	24 hours	+ + +

Each sign represents a ferret. + = Temperature and symptoms 0 = No sign of infection.

B.—The Relation between Circulating Antibodies and Immunity in Ferrets

[illegible] antibodies in human sera are dealt with in Section V, [illegible] human vaccination [illegible] of such antibodies present in a serum be accepted as an indication of the degree of resistance against infection enjoyed by the serum donor? It is upon the answer to this question that the proper exploitation of vaccine prophylaxis will largely depend

The fact that ferrets may possess considerable amounts of virus-neutralizing antibody and yet prove susceptible to infection has led some workers to doubt the importance of the serum antibodies in the immunity mechanism It was reported by Smith, Andrewes and Laidlaw (1935), however, that two completely immune convalescent ferrets had higher antibody levels than four artificially immunized ferrets which were shown to be only partially resistant.

Since that time, we have attempted to correlate antibody level and degree of immunity in a large number of ferrets treated in various ways.

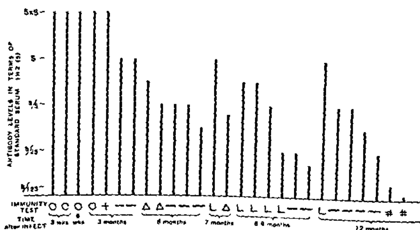
The samples of serum were obtained by cardio-puncture under ether anaesthesia. An immunity test usually followed immediately, but occasionally was delayed for two or three days. In most cases the test consisted in the intranasal instillation of a lung-adapted strain of virus under anaesthesia, but in two experiments contact with sick animals at the height of the disease was employed. Normal control ferrets were included in every experiment; with intranasal inoculation these invariably suffered a severe infection, and, at autopsy, showed very extensive lesions of pulmonary consolidation; with contact infection the controls always exhibited the typical ferret disease.

Antibody levels were estimated by titrating the serum samples in parallel with our standard immune horse serum by the mouse protection test, serum potencies being expressed as equal to standard, one-fifth standard (S/5) and so on. It must be emphasized that this method, although the best at present available, is a crude one with a considerable experimental error. A further source of discrepancy lies in the fact that accurate measurement of virus dose and virus virulence is impossible, so that a ferret shown to be immune by one test might possibly have proved non-immune had it chanced to be included in another test performed on a different day with more potent virus. These difficulties must be borne in mind for the interpretation of the results shown in the chart and tables.

1.—THE DECLINE OF ANTIBODIES WITH WANING IMMUNITY IN RECOVERED FERRETS

Chart 23 shows the results obtained with recovered ferrets at times after infection varying from 3 weeks to 12 months. There is a rough tendency for antibody level to be inversely proportional to length of time after infection, but the ferrets show much individual variation. Thus the lowest antibodies were found in the 12 months group, but one ferret belonging to this group had a serum equal to standard, actually more potent than any of the 6 months sera. It would appear that antibodies attain a high level very soon after the ferret's recovery, but begin to decline about 3 months later; the decline becomes more gradual as time goes on. Not all the animals were tested for immunity because some were required for the vaccination experiments to be considered later; those which were so tested confirm our earlier reports that complete immunity follows recovery from the disease and lasts for about 3 months; thereafter ensues the state of partial resistance in which the lungs are protected against attack by the virus (Smith, Andrewes and Laidlaw, 1935). It would appear that, with few exceptions, recovered ferrets with sera five times more potent than standard are completely immune and those with antibodies from S to S/25 are partially resistant, showing no lung lesions after intranasal inoculation and

being fully protected against contact infection. An antibody level of approximately S/125 indicates a return to complete susceptibility; at any rate in the two ferrets tested the responses were not appreciably different from those given by normal controls. The return to this condition of complete susceptibility may occur as early as 12 months after primary infection.



Each column represents a ferret   Height of column shows amount of serum antibodies

○ = ferret completely immune

+ = nasal symptoms following immunity test (No autopsy)

L = nasal symptoms following immunity test but no lung lesions at autopsy.

△ = ferret immune to contact infection

= no sign of resistance. Extensive lung lesions at autopsy

— = no immunity test carried out

Chart 23.

The relation of serum antibodies to active immunity in recovered ferrets

2.—The Effect of Vaccination on Ferrets with some Basic Immunity

It has been shown previously that ferrets which possess a low grade of basic immunity as a legacy from a previous attack of influenza can be rendered solidly immune again by vaccination (Smith, Andrewes and Laidlaw, 1935) A number of such ferrets were bled both immediately before and from 1 to 2 weeks after vaccination in order to estimate the increase of serum antibodies associated with the return to complete non-susceptibility

Vaccination consisted in either one or two subcutaneous inoculations of 5 c c. of a 5 per cent. or 10 per cent. suspension of infected

vaccinated ... been completely inactivated with formaldehyde. When two doses were

TABLE 33

The effect of vaccination on ferrets with basic immunity

Ferret	Duration of convalescence	Details of vaccination	Antibody level of serum			Result of immunity test		
			Before vaccination	*After 1st dose of vaccine*	*After 2nd dose of vaccine*	*Temperature*	*Symptoms*	*Lung lesions*
HF 28	7 months	2 doses living virus	S/25–S/5	5 × S	S–5 × S	0	0	Not killed.
HF 30	7	2 ,, ,,	S/5	5 × S	S–5 × S	0	0	,,
HF 16	9	2 ,, ,,	S/5	5 × S	>5 × S	0	0	,,
IF 818	8	1 dose ,,	S/25	5 × S		0	0	0
IF 828	8	1 ,, ,,	S/125–S/25	5 × S		+	+	0
IF 172	11	1 ,, ,,	S/5	S–5 × S		0	0	0
IF 87	15	1 ,, ,,	S/25	S–5 × S		+	+	0
IF 171	11	1 ,, formol vaccine	S/5	S–5 × S		+	+	0
IF 187	9	1 ,, ,, ,,	S/25–S/5	S–5 × S		0	0	0

given, a 12-day interval was allowed to elapse between them. Within a day or two of the final bleeding, each animal was tested for active immunity by the intranasal instillation under anaesthesia of a lung-adapted strain of virus. Normal controls were always inoculated similarly at the same time and these invariably suffered very severe attacks of influenza and showed extensive pulmonary consolidation.

The results obtained from 9 ferrets are given in Table 33. The antibody concentration before vaccination was between S/25 and S/5 in every case except ferret 828 which showed a somewhat lower value. Vaccination was followed by a striking stimulation of antibodies, ranging from something over a five-fold to more than a one hundred and twenty-five-fold increase. This varied response resulted in final antibody levels of remarkable uniformity, for only one animal (HF 16) showed a final value falling outside the range S to 5 × S; this was in the sample (>5 × S) taken after a second dose of vaccine. The other two ferrets which received a double vaccination had lower antibody concentrations after the second dose than after the first, which suggests that in some cases a maximum antigenic response will follow a single inoculation, provided there is already some basic immunity present, and that repeated inoculations may actually defeat the objective in view.

It appears that reinforcement of basic immunity is accomplished equally well with either living or formalin-inactivated virus

In only 6 of the ferrets was immunity fully restored by vaccination, in the other three the grade of resistance was insufficient to prevent infection, but sufficed to protect the lungs These results are in close agreement with those obtained in the case of convalescent ferrets in which 4 out of 5 ferrets with serum antibodies 5 × S were found to be completely immune, whilst the fifth animal showed symptoms following test inoculation

3.—Antibody Level and Immunity following Vaccination of Normal Ferrets

A number of experiments on the immunization of normal ferrets with the W S human strain virus are summarized in Table 34.

The variation in methods of immunization resulted in widely different antibody values ranging from 5 × S to less than S/125 One ferret (F 152) was completely immune to the test dose of virus and another (F 147) suffered only very mild nasal symptoms without any elevation of temperature. This indicates that vaccination of normal ferrets may result in a grade of immunity not far short of that required for the complete protection of the animal

The correlation between serum potency and degree of active immunity is further shown by the extent of lung involvement found at autopsy. All ferrets with serum antibodies >S/5 enjoyed practically complete lung protection (the ± signs represent minute lesions 1 to 2 mm. in diameter). Only 4 ferrets suffered extensive lung consolidation comparable with that exhibited by all the unvaccinated controls; all of them fall into the group with antibodies S/125 or

less. All animals with serum values between S/125 and S/5 posse
some degree of immunity, but
small lung lesions. Th
have been still closer i to test all the ferrets at
the same time with equal doses of the same virus suspension.

In 6 cases contact with sick animals was employed as the test for immunity. The 2 ferrets with most antibodies (S/5) proved immune; of the 4 with lower serum values, 2 were immune and 2 susceptible.

The ferret immunization experiments present features of interest apart from this question of relationship between antibodies and active immunity. The data in Table 34 offer some evidence as to the relative immunizing values for ferrets of different inocula, some derived from ferret, some from mouse tissues. It appears that living virus contained in mouse lung is at least as effective, if not more so, than living virus of ferret origin. On the
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although previously
against lung involveme
ferret vaccine (Smith, 1935). We do not wish to emphasize these results at present as the subject is being studied further. They contrast with our findings in mice in which vaccines made from infected mouse tissues are very much more effective than those made from tissues of another species (Andrewes and Smith, 1937) It is possible that the effect of source of vaccine may be overshadowed by other factors such as virus virulence and virus concentration of the various preparations and it is evident that much further study is required for the elucidation of these apparent inconsistencies.

4.—Cross Immunity in Ferrets following Infection with Different Strains of Human Influenza Virus

The experiments with various strains of virus isolated during the 1936–37 epidemic have been reported in Section IV Here it is only necessary to repeat that ferrets, after recovery from infection with one strain, may be actively immune to infection with heterologous strains although their serum antibodies against such heterologous strains are at a low level. It appears, therefore, that the relationship between antibody level and active immunity is more complicated than would appear from the work carried out with the single W.S. strain

C.—The Effect of Contact with Infectious Cases on the Maintenance of Immunity

In Section V we have discussed evidence which supports the hypothesis that the fluctuation in the average antibody level of the normal popula

sought more direct information by the following experiment on ferrets.

Eight ferrets were infected with our passage strain of virus After 2 months, when they had all fully recovered, 4 of them were exposed to contact with sick ferrets for a period of 24 hours and three further contact exposures were given at 2-monthly intervals. On none of these occasions did any of the animals show symptoms or igns of infection Meanwhile the other 4 ferrets were kept rigorously olated A fortnight after the final contact, all 8 ferrets were bled cardio-puncture and shortly afterwards were subjected to an immunity test consisting in the intranasal inoculation of lung-adapted virus under anaesthesia The results are given in Table 35.

TABLE 35

Effect of contact with infectious cases on maintenance of immunity

Ferret	Treatment during convalescence	Antibody level	Result of immunity test		
			Temperature	Symptoms	Lung lesions
63	Four contacts with sick ferrets at two-monthly intervals	S/5	0	0	0
65	" " "	S/5	0	0	0
73	" " "	>S	0	0	0
76	" " "	>S	0	0	0
67	Nil	S/5	+	+	0
68	Nil	S/25	+	+	0
77	Nil	S	0	0	0
79	Nil	S/5–S	0	±	0

There is a suggestion that the contact exposures might have had slight effect upon the antibody level, for the average level of the ntacted group is higher than that of the control group, the differ-es, however, are such as might very well be due to chance distri-ion into 2 groups of 8 ferrets with various amounts of antibody. result of the immunity test is more convincing, for all contacted ferrets showed complete immunity, whilst 3 of the non-contacted group developed symptoms It is surprising that an 8½ months convalescent ferret, F 77, and two ferrets with the low antibody level S/5, F 63 and F 65, should have proved completely immune. Possibly the immunity test was less severe than usual Nevertheless, 5 normal controls inoculated at the same time all showed severe symptoms and moderately extensive lung lesions

D.—The Relationship between Antibodies and Immunity in Mice

All workers are agreed that human and swine strains of influenza virus are related and probably possess certain antigenic components in common The precise nature of the relationship, however, remains to be elucidated Francis and Shope (1936) point out that an animal which has recovered from an infection with either human or swine virus may prove to be immune against the heterologous strain

less. All animals with serum values between S/125 and S/5 possessed some degree of immunity, but approximately half of them showed small lung lesions. There is little doubt that the correlation would have been still closer if it had been possible to test all the ferrets at the same time with equal doses of the same virus suspension.

In 6 cases contact with sick animals was employed as the test for immunity. The 2 ferrets with most antibodies (S/5) proved immune; of the 4 with lower serum values, 2 were immune and 2 susceptible

The ferret immunization experiments present features of interest apart from this question of relationship between antibodies and active immunity. The data in Table 34 offer some evidence as to the relative immunizing values for ferrets of different inocula, some derived from ferret, some from mouse tissues. It appears that living virus contained in mouse lung is at least as effective, if not more so, than living virus of ferret origin. On the other hand, formolized mouse lung vaccine was ineffective, in these experiments, although previously we had succeeded in conferring protection against lung involvement by vaccinating ferrets with formolized ferret vaccine (Smith, Andrewes, and Laidlaw, 1935). We do not wish to emphasize these results at present as the subject is being studied further. They contrast with our findings in mice in which vaccines made from infected mouse tissues are very much more effective than those made from tissues of another species (Andrewes and Smith, 1937). It is possible that the effect of source of vaccine may be overshadowed by other factors such as virus virulence and virus concentration of the various preparations and it is evident that much further study is required for the elucidation of these apparent inconsistencies

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strains are at a low level I
between antibody level an
than would appear from the work carried out with the single W.S. strain.

C.—The Effect of Contact with Infectious Cases on the Maintenance of Immunity

In Section V we have discussed evidence which supports the hypothesis that the fluctuation in the average antibody level of the normal population is due, at least in part, to contact with infectious cases. Since this evidence, derived from the examination of human sera, is inconclusive and entirely circumstantial, we sought more direct information by the following experiment on ferrets.

Eight ferrets were infected with our passage strain of virus. After 2 months, when they had all fully recovered, 4 of them were exposed to contact with sick ferrets for a period of 24 hours and three further contact exposures were given at 2-monthly intervals. On none of these occasions did any of the animals show symptoms or signs of infection. Meanwhile the other 4 ferrets were kept rigorously isolated. A fortnight after the final contact, all 8 ferrets were bled by cardio-puncture and shortly afterwards were subjected to an immunity test consisting in the intranasal inoculation of lung-adapted virus under anaesthesia. The results are given in Table 35.

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65	,, ,, ,,	S/5	0	0	0
73	,, ,, ,,	>S	0	0	0
76	,, ,, ,,	>S	0	0	0
67	Nil	S/5	+	+	0
68	Nil	S/25	+	+	0
77	Nil	S	0	0	0
79	Nil	S/5–S	0	±	0

There is a suggestion that the contact exposures might have had a slight effect upon the antibody level, for the average level of the contacted group is higher than that of the control group; the differences, however, are such as might very well be due to chance distribution into 2 groups of 8 ferrets with various amounts of antibody. The result of the immunity test is more convincing, for all contacted ferrets showed complete immunity, whilst 3 of the non-contacted group developed symptoms. It is surprising that an 8½ months convalescent ferret, F 77, and two ferrets with the low antibody level S/5, F 63 and F 65, should have proved completely immune. Possibly the immunity test was less severe than usual. Nevertheless, 5 normal controls inoculated at the same time all showed severe symptoms and moderately extensive lung lesions.

D.—The Relationship between Antibodies and Immunity in Mice

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TABLE 36

Relation between human and swine strain antibodies and active immunity in mice

Vaccine used	Group	Treatment before test	Treatment following vaccination	Result of immunity test					Antibody level	
				D	++	+	O	NS	Human.	Swine.
Human virus	1	Vaccinated	Tested with human virus	2		3	6	1		
	2	Nil	" " " "	8	2			2		
	3	Vaccinated	" " swine "	2		6	4			
	4	Nil	" " " "	7	3	2				
	5	Vaccinated	Bled for serum						S or >S	<S/125

Numbers under immunity test represent numbers of mice in following categories:—
- *D* = Specific deaths before termination of expt
- ++, + = Degree of lung involvement at autopsy
- *O* = Normal lungs.
- *NS* = Non-specific deaths

although it possesses no demonstrable serum antibodies against that strain. We have investigated this matter further by studying the effect of vaccination in mice upon the serum antibodies and the active immunity against both homologous and heterologous viruses.

Five groups, each of 12 mice, were used in an experiment with human strain (W S) vaccine. Three of the groups were vaccinated with a subcutaneous and an intraperitoneal inoculation of living mouse lung virus, an interval of 2 weeks being left between the inoculations. Two weeks later, the mice of one of these groups were killed to provide a pooled serum for the estimation of antibodies against both human and swine strain of virus. One vaccinated group and an untreated control group were given an immunity test with W S virus, the remaining two groups, vaccinated and control, were tested with swine strain virus.

The results, given in Table 36, show that vaccination was followed by active immunity against both human and swine strains of virus, and although the numbers are too small for rigid conclusions, they suggest that the resistance was only slightly better against the homologous virus. In contrast to this the antibodies against homologous virus attained a fairly high level whilst antibodies against heterologous virus were not demonstrable. The experiment, therefore, extends the findings of Francis and Shope to the immunity induced by vaccination, here also, just as in the immunity following recovery from infection, protection against a heterologous virus strain may be afforded although the serological response, as judged by our present methods of assay, would appear to be strictly homologous.

E.—Summary of Section VI

Previous reports have emphasized that the immunity induced in ferrets by vaccination is insufficient to protect them completely against the intranasal installation of virulent virus. The experiments recorded above show however that vaccination may fully protect against contact infection.

Some experimental evidence is presented in support of the view that contact with infectious cases may be a factor in the maintenance of immunity.

The results recorded indicate that in ferrets which have recovered from infection with, or been artificially immunized against, the W S strain of virus, there is a rough correlation between the antibody titre of the serum and the degree of active immunity. This suggests that if one could raise the antibody titre in human beings by vaccination one might expect to increase their resistance to infection. Unfortunately the situation is complicated by the existence of several serological races of virus. Francis and Shope (1936) and Shope (1937) have shown that animals recovered from infection with human virus may be immune to swine influenza and *vice versa*, even though they possess no demonstrable antibodies to the heterologous strain. Our experiments with mice support this conclusion. A similar anomaly,

probably, exists with regard to some of the different strains of human virus It is reported in Section IV that all ferrets infected with one or other of the 1937 strains of influenza virus were resistant when tested a few weeks later with W S. virus; yet such ferrets had but poor antibodies against W.S, equal as a rule only to S/25 or less. One might expect, therefore, on the basis of the animal experiments, that potent antibodies against a given virus strain in a human serum would indicate good active immunity against that strain, but that poor antibodies would not necessarily indicate low resistance.

SECTION VII

THE IMMUNIZATION OF HUMAN VOLUNTEERS

WILSON SMITH, C H. ANDREWES AND C. H STUART-HARRIS

Francis and Magill (1936a, 1937a) studied the antibody response of human subjects vaccinated with influenza virus They used living culture virus and inoculated volunteers either subcutaneously or intradermally with 3 doses at weekly intervals, a few were given a 4th dose 2 to 3 weeks later Whilst the antibody response varied in different individuals, all except one showed a considerable increase; this was not a gradual increase, but occurred fairly abruptly in the 2nd week. The high antibody level was maintained for 2 months, but after 5 months some decline was evident Individuals with a low initial antibody level responded more vigorously than those possessing much antibody before their vaccination Andrewes and Smith (1937) showed that a similar stimulation of antibodies follows either a single or a double dose of formolized mouse lung virus administered subcutaneously Stokes *et al* (1937) claimed to have reduced the incidence of influenza in a group of volunteers by intramuscular injections of living mouse lung virus, although only 31 per cent of them showed a rise of antibodies as a result of the prophylactic treatment They failed to recover virus from any case during the epidemic but only five cases were tested

It is highly probable from the American work that living virus is completely non-infective for man when inoculated parenterally. Shope (1936a), however, reported that although swine influenza virus had proved non-infective for swine when given by the intramuscular route under laboratory conditions, similar inoculations in the field were followed by cases of swine influenza in members of the herd left untreated All workers are agreed that vaccination with either culture or mouse lung virus, living or formalin-inactivated, produces no undesirable reaction apart from temporary smarting and occasionally slight local tenderness and swelling lasting for a day or two

Two of us discussed, in the publication cited above, the possible dangers of using living virus and, as the preliminary results obtained with formolized vaccine were promising, it was decided to extend the investigation along similar lines A study of the effect of vaccination upon serum antibodies was first made with a group of army volunteers obtained through the courtesy of Major General Perry and the army staff at Woolwich Later, several groups, each of about 100 volunteers, stationed in different localities, were vaccinated in the hope of demonstrating the efficacy of the treatment for the prevention of influenza during epidemics

A.—Preparation of Vaccine

Batches of young mice were infected with the highly virulent W.S strain of virus Only mice bred at the Medical Research Council's

Farm Laboratories at Mill Hill were employed. They were killed with chloroform 48 hours after inoculation and from the lungs filtrates were prepared by the method described by Andrewes and Smith (1937). The following tests were made on the filtrates

(1) Tests for bacteriological sterility with liquid and solid media and both aerobic and anaerobic methods.

(2) Titration of virus content by the intranasal inoculation of groups of mice with serial ten-fold dilutions. The filtrates were invariably infective at a dilution of $1/10^5$ or $1/10^6$.

(3) Tests for the virus of lymphocytic chorio-meningitis. This virus is known to be carried by many stocks of apparently normal mice and is pathogenic for man Six mice and two guinea-pigs were inoculated intracerebrally with filtrate and kept under observation for at least 10 days. In addition, we occasionally inoculated intracerebrally a few stock mice with sterile starch solution On no occasion did

6 days. A small sample was then removed, brought to pH 7·8 with dilute NH_4OH and tested for surviving virus by the intranasal inoculation of six mice These were killed 5 or 6 days later, and if all lungs were normal in appearance the main bulk of the vaccine was neutralized with NH_4OH, merthiolate 1/10,000 and issued for use On one occasion only was surviving virus found after 6 days' treatment with formalin so that a retest was necessitated after a longer period

varies, but is roughly 3 c c, a quantity of 2 c.c. was adopted as the dose administered subcutaneously to the volunteers

B.—Effect of Vaccination upon Serum Antibodies

1—Mouse Lung Vaccine

Sixty volunteers from the army personnel stationed at Woolwich

30 men, who were then vaccinated, 15 being given a single dose of 2 c c. and 15 two doses with a fortnight's interval between them. The vaccinations caused no general disturbance and only trifling local reactions consisting at most of a little local tenderness and swelling lasting for 2 or 3 days Two weeks after the completion of his vaccination, each man was again bled for serum All the serum samples were titrated by the mouse-protection test in parallel with our standard horse serum IH2 against the W S strain of virus The results are expressed graphically in Charts 24 and 25

The antibody levels preceding vaccination showed considerable variation, six sera were one-fifth as potent as the standard, whilst most of the others were less than a twenty-fifth. All the men showed a striking increase of antibodies following the vaccination: in most cases this was about twenty-five-fold, but in some of those with the higher initial antibody level it was only five-fold. The average level of the 30 volunteers after vaccination was about the same as we have found in most influenzal convalescents. There

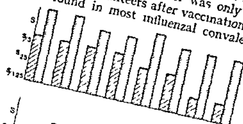


Chart 24

Antibody rise in men receiving one dose of vaccine

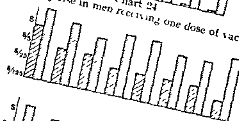


Chart 25

Antibody rise in men receiving two doses of vaccine

= levels of antibodies in sera, before vaccine

= levels of antibodies in sera after vaccination

was no significant difference in the response of the two groups so that a single dose of vaccine would appear to be as efficacious as two doses. This agrees with the experiments on ferrets reported on p. 128, and is almost certainly due to the fact that all the volunteers possessed some basic immunity.

Subsequently the sera from seven of the volunteers were tested against another virus strain (TAL) which had been isolated during the epidemic of December, 1936–February, 1937, and which was known to be antigenically different from the W.S. virus. A standard

serum against strain TAL was not available, but by including in the same experiment both the pre- and post-vaccination samples of each individual it was possible to estimate the increase of anti-TAL immune bodies consequent upon the vaccination with W S. vaccine.

The results are shown in Table 37, where the increases of W.S. homologous antibodies are also included for comparison. Six of the men showed a definite increase of TAL antibodies, but in every

ntibodies. Such

in view of the

man and swine

strains of virus it is possible to stimulate the production of the heterologous antibodies in swine, ferrets or mice by repeated inoculations with either strain. The most probable explanation is that W.S. and TAL strains contain antigenic factors in common. The stimulation of heterologous antibodies by vaccination may prove an important factor in the protection of the individual against epidemic infection

TABLE 37

Showing the increases of homologous and heterologous antibodies after vaccination

Volunteer	No of doses of vaccine	*Amount of antibody increase.* v W S virus (Homologous)	v TAL virus (Heterologous)
MI	2	5 or >5-fold	0 or <5-fold
CAS	2	25 ,,	5–25 ,,
ME	1	5–25 ,,	5 ,,
SH	1	>25 ,,	5–25 ,,
WE	1	5 ,,	<5 ,,
CAM	1	25–125 ,,	5–25 ,,
LI	1	5–25 ,,	5 ,,

2.—FORMOLIZED CULTURE VIRUS

It was felt that under certain contingencies, for example an epidemic in the mouse stock, a different source of virus for the preparation of vaccine might be required A preliminary experiment was made with formolized culture virus The culture strain had been carried through over 50 transfers on a medium of minced chicken embryo and Tyrode's solution by the technique described by Smith (1935) Several culture flasks were pooled, ground with powdered glass in a mortar, centrifuged at 3,000 r p m for 10 minutes to get rid of the glass and coarser tissue particles and then inactivated by treatment with formalin (1/5000 HCHO) for 5 days in the cold The product was tested to ensure bacteriological sterility and complete virus-inactivation before use Four volunteers were bled and then inoculated subcutaneously with 2 c c. of this vaccine, 2 weeks later further samples of serum were obtained

Only one of the four volunteers showed any appreciable rise of antibodies In this case there was approximately a five-fold

increase from S/5 to S This result is surprising in view of the excellent results obtained by Francis and Magill (1937a) with living culture virus and the fact that formalin-inactivated mouse virus is effective for the vaccination of both men and mice (Andrewes and Smith, 1937) It is probable that formalin treatment does reduce antigenic potency in some way and as cultures have a much lower titre than mouse lung filtrates, at any rate for mice, it may be that the formalin reduces their potency below the threshold necessary for the stimulation of antibodies

C.—Vaccination as a Prophylactic against Epidemic Infection

By the beginning of November, 1936, we considered that the results of our experiments on ferrets and mice justified a large-scale trial of the efficacy of human vaccination The absence of any epidemic of influenza in this country since the spring of 1933 gave a reasonable prospect that one might appear in 1937 The small-scale vaccination experiment at Woolwich, discussed above, was the first stage of the larger experiment planned, and as soon as the results were obtained, showing that antibody increase followed inoculation with our mouse lung formol vaccine, we set to work to make batches of the vaccine for the inoculation of volunteers

The plan of the experiment was to obtain several groups, each of about 200 volunteers, situated in widely separated localities so that some of the groups at least would probably come in contact with infection in the event of an epidemic of reasonable size. Apart from the staffs at the Medical Research Institute and Farm Laboratories, all volunteers belonged to army units In some groups half the men were inoculated and half kept as controls, in other army units all the volunteers were inoculated and the remaining men on the strength were regarded as controls

Unfortunately the epidemic appeared at Uxbridge in the middle of December, before sufficient vaccine could be prepared, tested and distributed Christmas leave also brought about further delay Nevertheless, it was considered advisable to proceed with the tests as it was impossible to foretell in which direction the epidemic would travel in the country and it was hoped that one or more of the chosen districts would escape infection until some time after the vaccine had been given to the volunteers This hope was not realized The results are analysed in Table 38 The case incidence was far too low for the figures to be of much value In every group except one (Aldershot 5) in which influenza appeared at all, the first case occurred either before or within 2 or 3 days of vaccination. In the Woolwich experiment in which vaccination had been completed some time previously, not a single case of influenza occurred in either inoculated or control groups The total numbers of the cases occurring from the actual date of vaccination are recorded in the last column, there are no significant differences between treated and control groups We know, however, that vaccination does not produce its antibody response until some time in the second

TABLE 38

The incidence of influenza in vaccinated and unvaccinated groups of human volunteers

Unit	Date of vaccination	Date of 1st influenza case	Group	No in group.	Influenza cases occurring after vaccination.			
					1st week.	2nd week.	After 14th day	Total
Windsor H G	28 12 36	12 12 36	Vaccinated	86	4	0	1	5
			Controls	115	3	1	1	5
Windsor F G	30 12 36 and 31 12 36	4 1 37	Vaccinated	95	0	2	2	4
			Controls	95	1	1	1	3
Aldershot W	16 1 37	14 1 37	Vaccinated	48	0	0	2	2
			Controls	125	2	10	3	15
Aldershot S	9 1 37 and 16 1 37	23 1 37	Vaccinated	89	0	0	0	0
			Controls	175	0	1	2	3
Colchester	9 1 37 and 12 1 37	6 1 37	Vaccinated	86	3	0	1	4
			Controls	86	2	2	0	4
Shorncliffe	7. 1 37	24 12 36	Vaccinated	93	3	0	0	3
			Controls	369	7	1	0	8
Duke of York's School, Shorncliffe	9 1 37	—	Vaccinated	103	0	0	0	0
			Controls	327	0	0	0	0
Institute and Farm Labs	30 12 36	20 12 36	Vaccinated	93	1	2	4	7
			Controls	61	1	2	0	3
Woolwich	10 11 36 and 24 11 36	—	Vaccinated	30	0	0	0	0
			Controls	30	0	0	0	0

week (Francis and Magill, 1937 a), and therefore judgment of its efficacy should be based upon case incidence in treated and untreated groups from about the 14th day onwards. In columns 7 and 8 are recorded the numbers of cases occurring from the 7th and 14th days after vaccination respectively. The figures are extremely small, but there is not even a suggestion of resistance having been conferred by the treatment. It must be borne in mind, however, that not all cases diagnosed as influenza were due to ferret-pathogenic virus. It was impossible to test garglings from every case, but 8 of the 10 cases which occurred amongst the vaccinated groups from the 14th day onwards were tested by ferret inoculation and 4 of them proved negative. Virus however was recovered from the other four, so that vaccination was certainly not completely successful in protecting against epidemic influenza of virus aetiology. This failure was possibly due to the fact that the strain of virus used for making the vaccine and the strains isolated during the epidemic were not antigenically identical. The existence of antigenic differences amongst strains was not known at the time of vaccination, the subsequent analysis of many of the freshly isolated strains is reported in Section IV.

As soon as it was realized that no conclusive answer would be obtained from the English experiment, we offered to supply vaccine to Dr. Taylor, of the Rockefeller Health Foundation, for trial in Hungary, which had, until that time, remained free from the epidemic. Dr Taylor carried out an experiment along lines similar to our own and he has given us permission to refer to his results, which are likewise inconclusive. The incidence of influenza amongst the groups chosen for the experiment was low, the epidemic began before sufficient time had elapsed for vaccination to exert its effect and the virus strains recovered from patients showed antigenic differences from the strain employed for the inoculations. Virus was recovered from one vaccinated individual who went down with influenza more than a fortnight after vaccination.

D.—Summary of Section VII

The experiments recorded in this section show that a striking antibody response follows the vaccination of human beings with even a single dose of formalin-inactivated mouse lung vaccine. In contrast to this only one of four men inoculated with formalinized culture virus showed any appreciable increase of serum antibodies, although Francis and Magill (1937 a) obtained good results with living culture virus. The explanation of these apparent discrepancies must await further experimental investigation, meanwhile caution is necessary in correlating and applying the results obtained with vaccines prepared in different ways and from different species of animal.

Our experiments have failed to yield the conclusive evidence which we hoped to obtain regarding the efficacy of prophylactic vaccination against epidemic influenza. This failure was largely

recently received some experimental support by the work of Francis *et al.*, (1937 d), who have shown that pneumonia may, during an influenza epidemic, attack patients who already have a high virus antibody content in their body fluids. The antibody level did not rise, as is the rule in the virus disease In these cases it would appear that the virus had no direct influence in the development of the pneumonia but that pneumonia attacked a patient whose resistance to pneumococcal infection had been lowered by a successful struggle with the virus disease.

There remains a group of pneumonia cases where the rôle of the virus is not so surely known owing to the fact that it was only recovered with certainty in one case. The high level of virus-neutralizing antibodies during convalescence, however, renders it probable that these were mixed infections with virus and bacteria.

It is abundantly evident that much further work is required on the more severe cases of epidemic influenza and particularly cases with lung complications, including all the varieties of pneumonia The evidence from this one outbreak is [illegible]

available for the identification of the virus are clumsy and costly, while it is impossible to keep clinical, bacteriological and pathological staffs in being, and fully equipped, for the study of an epidemic which is so erratic in its appearance, so capricious in attack, and which lasts for such a short period in any one locality. It is also exceedingly difficult to arrange that clinicians, bacteriologists and pathologists shall be set free from routine duties whenever an influenza outbreak occurs and thus allowed to devote all their energies to the study of the epidemic disorder Yet without some such elaborate arrangement, progress in the analysis of complicated cases of influenza in man is bound to be slow. Some recent work by Francis and Magill (1937 b and c) and Hyde and Chapman (1937) indicates that it may be possible in the future to isolate strains of virus from man by employing mice or chick embryos in the place of ferrets, and if this technique proves to be generally successful, one of the major difficulties in the laboratory diagnosis will have been removed

Systematic blood counts on 38 uncomplicated cases of the virus disease, have shown that, in the acute stage of the illness, the white blood cell count was within normal limits, and such counts are, therefore, not of great assistance in the diagnosis

The laboratory investigations which were made in parallel with the clinical observations have yielded information of great interest. First—influenza virus, pathogenic for ferrets, has been recovered from a high proportion of typical cases of influenza during the epidemic of 1936–37 The strains of virus appear to be very similar to those obtained in previous years, in this country and in other parts of the world, because they are all neutralized by our standard hyper-immune horse serum and they cannot be readily distinguished

by means of cross immunity tests in ferrets Virus was not obtained from cases of "febrile catarrh," which resembled influenza to some extent in symptomatology (pp 19, 24 and 27) The findings of ourselves and others in previous epidemics are thus abundantly confirmed, but although the viruses are all closely related, recent studies have shown that different strains occur, as was first pointed out by Francis and Magill, and the study of the 1937 strains has made it clear that these show differences from those obtained in previous years, and also that all the 1937 strains are not identical We do not yet know how many strains of virus we may have as it is a slow and tedious task to analyse the whole group The multiplicity of strains of virus is clearly a very important matter from the point of view of *prophylaxis and epidemiology, and it will be referred to again*

Secondly—a great deal of work was done in studying the antibody content of human sera, as measured against our passage strain of virus (W S), before we were aware that several strains of virus existed, and looking back it is clear that much further valuable information could have been secured if we had had at our disposal a number of type-strains of virus However, it seems clear that the general level of neutralizing antibodies for W.S virus fell in the general population to a fairly low level by the end of 1936. Neutralizing antibodies to the W S virus may develop in patients who suffer infection from one of the other kindred strains This is hardly surprising since the experiments with hyper-immune horse serum show that there is some common factor in all the strains so far studied Indeed there is good evidence to show that antibodies to swine influenza may appear after infection with the human strains of virus Evidence has also been obtained that neutralizing antibodies may develop in influenza contacts who themselves show no sign of infection No proof could be obtained that there was any relationship between the level of neutralizing antibodies for the W S. virus in human sera and susceptibility to infection during the last [illegible]

single strain are of considerable interest

Experiments on the immunization of ferrets against our passage (W S) virus have been described previously In this report it is shown that although it is not possible to immunize normal ferrets completely against massive test doses of virus, yet it is possible to render them sufficiently resistant to withstand the milder test of contact infection with the same strain of virus Further, numerous [illegible]

encouraging as their application to man is self-evident, and tests on volunteers were planned and commenced. Francis and Magill, however, pointed out that all virus strains were not identical, and this fact, which has been confirmed and extended by the study of

new and older strains, creates difficulties in devising efficient vaccination prophylactics. In Section IV it is recorded that active cross-immunity experiments show that, although vaccination of mice with one strain will render them resistant to that strain, they are only partially resistant to a different one. Further, the virus-neutralizing potency of a serum, though a rough measure of a ferret's resistance to the homologous virus, does not measure, even crudely, the resistance to a heterologous strain

Vaccination of human volunteers with formolized W.S vaccines was undertaken on a fairly large scale, and it is shown that such vaccination raised the level of circulating antibodies against the strain of virus from which the vaccine was prepared, in all cases which were tested. Many of the volunteers received the vaccine too late to allow of any deduction being drawn as to the efficiency or otherwise of the method of prophylaxis The majority of the vaccinations were done after the epidemic had commenced and an interval of fourteen days between vaccination and exposure to infection is required before any just conclusion can be drawn as to the value of vaccination of this kind. However, there were four cases of influenza, of proven virus aetiology, in volunteers who had been vaccinated more than fourteen days previously, which proves that the method of vaccination employed failed to confer adequate protection in some of the men. Almost all the virus strains recovered during the last epidemic show differences from the W S strain, and the only strain recovered from a vaccinated subject and thoroughly studied is certainly not identical It is thus clear that the possibility, or otherwise, of successful protective vaccination of man has not been tested properly. The multiplicity of strains once more creates difficulties for the pathologist, though probably it will be of assistance to the epidemiologist

It will be obvious that much of the work herein recorded was done with the original W S. virus before it was recognized that varieties of influenza virus existed, and it is hoped that repeated reference to virus strains, and the emphasis that is laid on the fact that what holds for one strain may not be applicable to the group, has not proved too distracting It was thought well to place the findings on record at this stage because the virus strains are certainly close relations, and what holds for one strain will probably be applicable to any other one, to postpone reporting until all virus strains had been studied, and their inter-relationships established, would probably have resulted in undue delay.

It is very easy to overestimate the importance of Magill and Francis' discovery of differences in strains. It is equally easy to belittle the differences At the present time it is impossible to form a just appreciation of the difficulties to be met and the amount of work necessary in the future. It is clear that all the strains have some common factor and the differences, so far as present information is available, are not so great as is the case with certain other viruses such as the three strains of foot-and-mouth disease It is clear,

however, that the differences may be large enough to influence, very unfavourably, a vaccination experiment (p. 110). For the future it is evident that it is desirable to ascertain, first of all, the main antigenic groups, keeping well in the foreground the factors which influence active immunization against infection. There are indications that the strains overlap to a considerable extent and it is just possible that a strain exists which will cover all types sufficiently well to render immunization with mixed vaccines, or successive inoculation with vaccines made from 3 or 4 strains, unnecessary. A full analysis of all strains, and the relationships of one to the other and also to the swine virus, though very interesting and important in many ways, is probably of lesser utility from the point of view of prophylaxis.

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